Psychiatric Intervention Pre & Post Bariatric Surgery

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Abstract

The burden of obesity and related medical and psychological problems is huge worldwide and India is among the worst affected countries. Bariatric surgery (BS) is the mainstay of obesity treatment (BMI>40kg/m2 without or BMI>35kg/m2 with medical complications) and related medical comorbidities (type-2 diabetes, cardiovascular diseases, etc). It not only improve physical morbidities, but also psychological morbidities (depression, binge eating ds., low self-esteem, and health-related QoL, etc.). Pre- and post-surgical assessment of these psycho-social factors, particularly by a mental health professional (MHPs), facilitates better post-surgical physical outcomes and psychosocial adjustments. Similarly, interventions (psychoeducation, Cognitive behavioural therapy, behavioral interventions, etc.) targeting at-risk prospective recipients of surgery or those who underwent surgery (having psychosocial issues, poor motivation to comply with the dietary and exercise regime, binge eating patterns) improve their physical and psychosocial functioning. However, the improvement is restricted to 1-2years post-surgery, while long-term positive outcomes are still lacking. Despite the significant evidence-base on the role of psychological assessment and interventions in BS, it is hardly exercised in routine clinical practice. This could be attributed to lack of sensitization among the surgeons, stigma associated with mental problems/illness, fear of such process resulting in an undue delay in surgery, and MHPs often being part of the multi-disciplinary team providing care to individuals undergoing BS. This is compounded by the lack of a clinical practice guideline (CPG) in our country. Hence, This CPG is aimed at developing a protocol for the psychological assessment and management of individuals seeking BS.

1. Introduction

Obesity and related complications are endemic throughout the world, including in India. India accounts for 1.37billions of obese individuals.[1] While non-pharmacological and non-surgical mode such as caloric restriction, exercise, and behavioral modification have been the mainstay of management of overweight to obesity with BMI<30kg/m2, these strategies have not been found to useful in sustained long-term weight loss in the severely obese individuals (BMI≥40).[2] Asian populations, particularly, are at increased risk of developing centripetal obesity, which is a risk factor for the development of type-2 diabetic Mellitus (T2DM) and other metabolic-syndrome related-complications. Obesity and Metabolic Surgery Society of India (OSSI) guideline (2020) suggests that Bariatric/metabolic surgery should be considered a treatment strategy for acceptable Indian patients with a BMI ≥ 35 kg/m2 with or without the presence of any obesity-related co-morbidity/ies and individuals with a BMI≥ 30 kg/m^2 having two or more obesity-related medical comorbidities.[3]

Given this, bariatric surgery has become a vital strategy to manage severe obesity. India has become a hub for such surgeries just following the United States and China. Research suggests that bariatric surgery not only results in weight loss but also improves the medical (T2DM, cardiovascular diseases, etc.) and psychological problems/comorbidities (depression and suicide attempt, quality of life [QoL], binge eating disorder, etc.) among the recipient of surgery.[4] Commonly used Bariatric surgeries are categorized into restrictive type[5] (Sleeve gastrectomy), malabsorptive type (Roux-en-Y-gastric bypass (RYGB)), and combined (malabsorptive and restrictive) approach (One anastomosis gastric bypass (OAGB)/mini-gastric bypass).[2] It has been posited that the mental health problems seen in individuals seeking bariatric surgery (or are associated with obesity) are the outcomes of obesity rather than the cause of obesity. Therefore, the benefit of bariatric surgery is not only restricted to significant improvement in physical parameters, but also significant improvement in affective symptoms, anxiety, binge eating disorders, QoL, etc.[6]

However, the success of surgery lies in a sound pre-surgical patient screening, including the psychological assessment (psychological problems/comorbidities, social support, motivation, and ability to cope-up with the post-surgical demands). Nevertheless, psycho-social assessment of individuals being planned for the bariatric surgery is a less-opted path in clinical practices; often is performed merely to fulfil the requirement of an insurance agency. The practice of

non-performing routine psychological assessment of these individuals is also due to lack of standard guidelines-both from surgery and mental health- on approach to pre- (or post-surgical) psychological assessment, fear on part of patients of getting rejected for surgery or undue delay in getting surgery, stigma (both patient and surgeon) and lack of orientation of the bariatric surgery-team about the mental health needs of the individuals seeking bariatric surgery and post-surgical adjustments.[5,6]

2. The rationale of the guideline and its scope

In the absence of a clinical practice guideline (CPG) on the psychological assessment of the individuals seeking bariatric surgery or have undergone surgery for their post-surgical surgical adjustment, a formal assessment protocol is not in place in majority of the healthcare facilities involved in performing such surgeries in India. Moreover, as there is conflicting evidence regarding the effectiveness of such assessments and impact of various psycho- behavioural interventions on post-surgical physical and psychological outcomes, such practices have not been promoted as well as adopted in the field of bariatric surgery. The current CPG is aimed at reviewing the current level of evidence on the psychological issues among the individuals seeking bariatric surgery, the impact of pre-and post-surgical psychological problems on the post-surgical outcomes, and, also, of the effectiveness of pre-and post-surgical psychological interventions on the post-surgical outcomes. However, this guideline does not claim to be the one-size-fits approach in all health settings, and its practice should be tailored according to the patient population, institutional practices, and available resources.

3. Psychological issues among individuals seeking bariatric surgery

Literature suggests that individuals seeking bariatric surgery often suffer from depression (suicidality), Binge Eating Disorder (BED), and had experience childhood-sexual abuse (CSA), including personality issues.[7] Additionally, they face significant stigma (including perceived stigma), suffer low self-esteem, sexual dysfunctions, relationship issues with the spouse/partner, insomnia, cognitive problems, poor coping skills (often eating is a maladaptive way of coping), body image concerns. Consequently, have poor Health-related quality of life (HRQoL) (Table 1).[8]

These psychological risk factors can worsen the pre-and post-surgical medical comorbidity/es. On the contrary, timely and effective addressal of these issues can result in a significant reduction in medical complications and frequent post-surgical hospitalization.[9] Therefore, the psychological issues of such individuals should be identified and resolved during the pre-surgical evaluation stage and to be monitored in post-surgical recovery stage as well and managed, if required.

Table 1. Prevalence of psychiatric disorders among the individuals seeking bariatric surgery

Psychiatric condition	Prevalence (pooled estimate†, 95% CI)
Any mood disorder	23 (15-31)
Depression	19 (14-25)
Binge eating disorder	17 (13-21)
Anxiety	12 (6-20)
Suicidal ideation or suicidality	9 (5-13)
Personality disorders	7 (1-16)
Substance abuse disorders§	3 (1-4)
Psychosis	1 (0-1)

† pooled estimate is based on random-effect meta-analysis, CI: confidence interval

§ does not include nicotine dependence syndrome

Adopted from (Dawes AJ, Maggard-Gibbons M, Maher AR, et al. Mental Health Conditions Among Patients Seeking and Undergoing Bariatric Surgery: A Meta-analysis. JAMA. 2016;315(2):150–163. doi:10.1001/jama.2015.18118**)**

4. Pre-surgical psychosocial assessment of individuals seeking bariatric surgery

The goal of pre-surgical psychological assessment is not limited to identifying any psychiatric illness, but to evaluate the mental health stability of the patients to undergo surgery, to assess their level of motivation for the surgery, evaluating their level of the adherence to the pre-surgical lifestyle modifications (LSMs, exercise, dietary modifications, etc.) and factor influencing them, and comply with post-surgical recommendations, including the ability to cope-up with the post-surgical physical, psycho-social, lifestyle stressors/demands (Table 2).[5]

A psychologist (or MHP) should be trained in medical psychology as there is often a complex interplay of obesity, medical comorbidities, psychological problems, and post-surgical adjustments or complications.[6]

The psychological assessment should also include post-surgical relationship issues and potential source of stressors (job-related, treatment-related, change in the dynamics of the relationship, etc.). According to some international guidelines (Brazil, The United States), psychologists and/or psychiatrists of the multidisciplinary team should ensure the absence of substance use disorders (SUDs), psychotic disorders, and dementia.[6,10] Further, they are also responsible for guarantying that patients have the intellectual and cognitive capacities to assess the risks associated with the surgery and the special care needs that are warranted subsequently.[6]

Additionally, support group (psychoeducation about the surgery and potential outcomes, sharing of the psychological and physical concerns with other individuals seeking bariatric surgery, post-surgical changes, and needs, etc.) under the supervision of a nurse or counselor even before surgery, and motivational interviewing (exploring patients their level of motivation, expectation, unreasonable or unattainable goals and help them arrive at more moderate ideals.) have been found to improve post-surgical adjustment (both physical and psychological). However, these interventions have not been tested in a randomized-controlled design (Table 2).[11]

A thorough clinical interview should be conducted to evaluate persons' personality issues, including level of impulsivity, binge-eating disorders, co-morbid depressions, anxiety disorders, etc. as they can adversely affect their compliance with the recommendations of the treatment team. Moreover, certain personality factors result in greater level of non-satisfaction with the surgical outcomes and poor-therapeutic relationships with the treatment team. The clinical interview should be supported by the application of special psychological testing should be performed (Beck Depression Inventory, the Minnesota Multiphasic Personality Inventory, Binge Eating Scale). There are specific interview schedules, that could be modified as per the cultural and institutional requirements (Boston Interview and the PsyBari) (Table 2).[12,13]

If the psychologist or MHP deem that the person lack capacity (to understand the risks, benefits, and results of the surgical procedure; a reluctance to adhere to the postoperative recommendations) or has certain psychiatric illnesses (active psychosis, mood disorder,

multiple suicide attempts or a recent suicide attempt, addiction, dementia, severe mental retardation, severe life stressors) surgery should be postponed or rescinded.

Table 2. Components of pre-surgical psychological assessment

Succinctly describing the purpose of evaluation: allaying the misconception and prejudices related to psychological assessment (purpose to help the patient rather deeming them unfit)
Assessing knowledge and attitude: their understanding about the surgical procedure and its outcomes, including their level of expectation
Assessing current and past mental health functioning: assessing for all major psychiatric illnesses, particularly depression, BED, impulsivity, SUD, psychosis, personality ds. Etc. How symptoms were managed? (Types and setting of treatment) and their perception about the improvement with it.
Stress and Coping Skills: Level of perceived stress and mood in the last *6m-1yr* and their coping techniques (problem- vs emotion-focused) (particularly eating as a coping method). Their perception about upcoming stress (relationship issues, physical changes, etc.) and prospective coping strategies
Social support: level of social support they have and would need post-surgery towards treatment, including post-surgery follow-ups, and daily-life-related changes
Cognitive and Social Functioning: level of cognitive functioning (memory, attention, and concentration, comprehension [MMSE], planning, impulse control, motivation) and social skills (interpersonal skills, including communication with the treatment team, etc.)
Motivation: motivation towards surgery, reason to undergo surgery, locus of motivation (internal/external), comply with the recommendations, and behavioral changes required, etc.
Monitoring their compliance with the lifestyle modification: Monitoring their compliance with LSMs and factors (including psychosocial factors) influencing them
Objective Psychosocial Measures: Eating disorder (Binge Eating Scale, TFEQ), depression & anxiety (PHQ-9), personality (MMPI), QoL (WHO-QoL-Bref/ IWQOLLite)/ SF-36), coping skills (stress-coping behavior scale, proactive coping inventory)
Preparing a report to the surgical team: fitness for surgery, factors (risk and protective factors) influencing patients pre-and post-surgical adjustments, flagging*****, need for pre-or post-surgical non-pharmacological/ pharmacological interventions.

IWQOLLite: Impact of Weight on Quality-of-Life Questionnaire-Lite; *****Flagging refers to because of certain bio-psycho-social vulnerabilities patients should be observed more closely during the follow-up period); MMSE: mini-mental state examination, Minnesota multi-phasic personality inventory; SCBC & PCI are validated in Indian population; SF-36: symptoms checklist-36**;** TFEQ: Three-Factor Eating Questionnaire; WHO-quality of life-brief scale.

5. Post-surgical psychological consequences

a. Assessment

Apart from improving the medical aspects of obesity and related comorbidities, bariatric surgery through a direct biological mechanism also brings about a positive psychological change among the recipients of surgery, an improvement that occurs irrespective of pre-surgical psychological interventions (Table 3). For instance, long-term assessment of bariatric surgery-2 (LABS-2) study involving 2,036 patients who were followed for 5 years found that among the cohort who were initially not satisfied with their sexual lives, post-surgery, 56.0% of women and 49.2% of men experienced clinically meaningful improvements at year 1 which also persisted till the 5 years of follow-up .[7] Similarly, longitudinal studies have reported a significant improvement in depression (both prevalence and severity) following the bariatric surgery that persisted till 1-3years after surgery, however, after which the effect wanned-off.[14,15]

Further, longitudinal studies suggest that individuals undergoing bariatric surgery have a higher risk of suicidality compared with patients who were provided treatment as usual or those treated with intensive LSMs.[16] The suggested reasons were unsatisfactory weight loss post-surgery, malabsorption of essential nutrients resulting in depression, impulsivity/intoxication due to altered pharmacokinetics (greater absorption of alcohol and other drugs) of substances, etc. Also, as post-surgery, the prevalence of indulgence in self-harm behaviors are higher than the general population, though this could be attributed to pre-surgical bio-psycho-social vulnerabilities of suicide and self-harm. Notably, the risk of suicide decreased post-surgery, at least in the initial one year, has been found to be lower than the pre-surgical period.[7]

Regarding substance use disorders, longitudinal studies have reported after RnYGB surgery among those with pre-existing abnormal eating patterns (e.g., BED), there has been an increase in the prevalence of alcohol use disorders (addiction transfer-model), altered reward circuitry, and altered metabolism of alcohol.[17] Similarly, this altered reward model (though lacking empirical validation) could also result in an increased illicit substance use and other substance use disorders with as high as 7.5% and 4.9% of participants reported incident of SUDs within 5years post-RYGB and post-adjustable gastric banding respectively.[7] This also holds for the overuse of opioid analgesics. Despite this, substance use and related problems post-surgery are often under-identified and undertreated. This warrants a more thorough assessment of substance use and related problems among the recipients of bariatric surgery.

Furthermore, LABS-2 study involving 1,159 patients with 4 to 5 years of follow-up found that post gastric bypass, patients reported modest degrees of being bothered by excessive skin, primarily in their waist/abdomen, thighs, and chest/breasts body areas. Being female, young, and having severe obesity is associated with a higher level of dissatisfaction, perceived disfigurement, and depression post-surgery, which required out-of-pocket expenditure. Furthermore, Hence, post-surgical psychological assessment, thus, intervention should aim to address this.

Post-surgery, peak improvements in HR-QoL outcomes were noted during the initial first year up, which is followed by a gradual decline till 5years, at which it got stabilized, these findings have also been supported by a systematic review (involving 19 prospective cohort studies).[18] Nevertheless, HR-QoL remained improved, relative to the preoperative QoL, but remained below that of the general population. Similarly, longitudinal studies revealed that neurocognitive functions (memory, executive function) improved post-surgery.[19,20]

Longitudinal studies, Swedish Obese Subjects (SOS), and the Scandinavian Obesity Surgery Registry (SOReg) revealed that bariatric surgery-induced weight loss is associated with a greater likelihood of change in relationship status. While a single individual opting for a marriage or a new relationship, married individuals experience an increased incidence of divorce and separation. Thus, patients may be counseled preoperatively and made aware of the potential relationships changes post-surgery and their impact on patient's life.[21]

Similarly, pharmacokinetics of the psychotropic medications can significantly change post-surgery. For instance, the transit time of certain drugs may be increased following sleeve-gastrectomy (leading to greater or lesser absorption of medications) or altered rate of absorption of Lithium (increased dissolution of extended-release preparations of Lithium and subsequent rapid absorption of the drug, resulting in Lithium toxicity), SSRIs, and SNRIs post-RYGB surgery Altered Area Under the Curve for SSRIs and SNRIs
To summarise, although current level of evidence does support the short-to-medium (up to 2yrs) benefit in psychiatric outcomes post-surgery, there is no long-term benefits (2-7years).

Table 3. Post-surgical psychological aspects of the individuals received bariatric surgery

Sexual functioning: usually post-operatively an improvement in sexual functioning of the patient is seen, however, it should be assessed for emergence of new symptoms.
Substance Use: Possible increase in substance use (including opioid analgesics) post-surgically, hence must be assessed routinely.
Psychosocial function and HR-QoL: an increase in marriage and new relationship; paradoxically, also, an increased rate of divorce/separation[#] also seen)
Neurocognitive functioning: Improvement, including in memory and executive function
Status of pre-surgical psychiatric problems/illnesses: Improvement in BED, depression, anxiety (though anticipatory anxiety[##] can emerge), self-harm, and suicidality, etc.
Re-emergence of psychiatric illness/symptoms: usually following 2-7years after the surgery (BED, depression, suicidality, etc.), including disillusionment (loose skin, etc.)
Change in the pharmacology of the psychotropic medications: the transit time of drugs may be increased following sleeve-gastrectomy (leading to greater or lesser absorption of medications) or altered rate of absorption post- RYGB surgery (Li, SSRIs, SNRIs, etc.).

[#] Due to leaving old unsuccessful and maladaptive marriage upon gaining self-esteem post-surgery; [##]after surgery secondary to dumping syndrome, etc.], AUC: area under the curve, resulting in differential effectiveness and toxicity; HR-Qol: health-related quality of life; SSRIs: selective serotonin reuptake inhibitor and SNRIs: serotonin-non-epinephrine reuptake inhibitors.

6. Post-surgical psychological evaluation of recipients of bariatric surgery

The goal is to assist recipients of bariatric surgery in their unique needs throughout the course (short as well as long-term) of recovery. However, there is no clear-cut guideline pertaining to post-surgical psychological assessment of recipients of bariatric surgery. Kinzel (2020) suggests that regular psychological sessions (such as change of self-esteem because of weight loss, problems in adopting new eating behaviors and the risk for developing a new eating disordered behavior, and problems involving adequate problem-solving) result in good post-surgical psychological and physical adjustments. However, this needs to be investigated in controlled trials.[22]

Similarly, there is RCT involving individuals undergoing LABG that suggest post-surgical assessment such as accurate case history, clinical examination, precise analysis of eating behaviors, and a psychological evaluation to assess the patient's compliance after the operation, including correcting compulsive eating habits, coping with the anxiety following surgery, etc., results in a good post-surgical outcome such increased weight loss, early and late

complications, and lesser band calibrations and LABG inflation in weight.[23] Thus the psychological assessment must be in place post-surgery to evaluate the recipients' level of motivation and capability to adhere to the recommendations of the surgical team (avoiding compulsive eating, adhering to dietary and exercise regimen, etc). Also, to cope up with the psychological (anxiety, relationship issues, dissatisfaction, less than desirable response to surgery, etc.) and physical challenges post-surgery (disfigurement).

Table 4. Post-surgical psychological assessment of recipients of bariatric surgery

Perception of the patients about outcome of the surgery: Patients' perception about improvement in both physical (weight loss, eating pattern, etc.) and psychosocial (low mood, self-esteem, HRQoL, etc.) parameters following surgery, including level of satisfaction/dissatisfaction, and expected long-term outcome of surgery should be assessed.
Status of pre-surgical psychiatric illness: The status of pre-surgical psychiatric issues **(**depression, BED, Anxiety, personality issues, body-shape concerns, self-esteem, stigma, etc.) should be assessed.
Attitude and motivation towards post-surgical treatment: Their attitude and motivation for the demands of post-surgical treatment and LSMs needs to be assessed.
Dynamics of their relationship: The change in their relationship with spouse/partner and significant others and its influence on treatment adherence should be evaluated.
Upcoming stressors: Job-related changes and possible future stressors should be assessed.
Social support: Availability of current level of social support to meet the demands of treatment and daily life affairs should be assessed.
Coping methods: Their coping methods for any upcoming stressors should be evaluated.
Attitude and willingness to follow-up with the treating team: Their attitude and level of motivation to regularly meet the surgery team (including dietician, MHPs [particularly among those with pre-existing mental health concerns], etc.).

BED: binge eating disorders; HR-Qol: health-related quality of life; LSMs: lifestyle modifications, MHPs: mental health professionals

7. Association of pre-surgical psycho-social characteristics of the individuals seeking bariatric surgery and post-surgical outcomes

There is insufficient evidence to determine the relationship between preoperative mental health conditions and postoperative weight loss outcomes.[7,8] Systematic review and meta-analysis have shown that pre-surgical psychiatric illness/problems (depression, BED, suicide, childhood sexual abuse) have not been found to have any significant impact on post-surgical weight loss. [7,8]

8. Interventions

Management of psychological problems among the individuals undergoing or undergone bariatric surgery involve lifestyle and behavioural modifications, non-pharmacological interventions, and pharmacological interventions in select group of patients.

I. Pharmacological interventions:

It's not uncommon for the obese patients being considered for the bariatric surgery (and post-surgically as well) to suffer from clinical depression, anxiety, BED, impulsivity, or other psychiatric disorders. These illnesses could be an outcome of the obesity or co-morbid with the obesity. Since psychotropic medications used to treat these conditions may worsen the obesity and associated medical comorbidities, they should be used only when required that too agents which are less likely to cause weight gain or metabolic syndrome. A detail about the choice of the drugs for various psychiatric disorders based on their propensity to cause metabolic or cardio-vascular adverse effects have been tabulated in Table 5.[24,25]

Management of depression:

It is recommended that individuals with mild-to-moderate depression to be primarily managed with the non-pharmacological interventions such as interpersonal therapy, CBT, supportive therapy, etc., particularly, when there are significant psycho-social stressors, intrapsychic conflicts, or interpersonal difficulties.[26] However, antidepressants may be used as an initial treatment strategy in mild, moderate, and often, severe depression, especially when there is history of prior positive response to antidepressant medication, presence of severe symptoms, significant sleep and appetite disturbances, agitation, or anticipation of the need for maintenance therapy. Patients with severe depression with psychotic features will require use of combination of antidepressant and antipsychotic medication and/or ECT. The choice of the medications is determined by the severity of the depression, safety profile of the medications and tolerability (Table 5).

Management of Anxiety disorders:

Likewise of depression, obese patients with mild-to-moderate level of anxiety disorders (generalized anxiety disorders, panic disorders, phobia, obsessive compulsive disorders, etc.)

should be managed with the non-pharmacological interventions such as relaxation exercises (Jacobson's progressive muscle relaxation, behavioural therapy, biofeedback, etc.), CBT, systematic desensitization methods, etc.. Anti-anxiety medications, however, are indicated when the anxiety disorders are severe, previous history of response to medication, presence of significant vegetative or autonomic symptoms, incomplete remission with the non-pharmacological interventions. The choice of anxiolytics should be based on relative propensity of these agents to alter the metabolic profile and weight of the individuals (table 5).

Management of the binge-eating disorders:

The BEDs often are comorbid with the depression, OCD, impulse control disorders, etc.. The management of the BED involves a multi-pronged approach that include nutritional rehabilitation and counselling, psychosocial interventions (motivational interviewing, CBT, IPT. Etc.), and medications. The drugs that have been found to be effective are 1) antidepressants like SSRIs (higher than those used for depression, e.g., fluoxetine 60 mg/day; Sertraline has also found to be effective), however TCAs and MAOIs should be avoided, 2) anti-convulsant (topiramate; lamotrigine, and Zonisamide for impulsivity; etc.), when other drugs are ineffective. On contrast, mood-stabilizers such as lithium and valproate to be avoided for it can cause significant weight gain (Table 5).[27]

Table 5. Psychotropic medications and their propensity for weight gain, dyslipidaemia, diabetes mellitus, and hypertension

Drug category	Obesity	Dyslipidaemia	Diabetes	Hypertension
Antidepressants				
Bupropion	-	- (if l/t wt. loss)	?	+
SSRIs, SNRIs	?	?	-/0	0 (SSRIs)/+ (SNRI)
TCA, Mirtazapine, paroxetine	+	0 to + (if l/t wt. gain)	++ (TCAs)	+ (TCAs)
Anxiolytics				
Paroxetine, TCA, Mirtazapine	+	0 to + (if l/t wt. gain)	++ (TCAs)	++ (TCAs)
SSRIs, SNRIs	?	0	-/0	-/0
Buspirone, anti-adr., Benzodiazepines	0	0	0	0/ - (anti-adr.) 0
Pregabalin	?	?	?	?
Mood stabilizer†				
Lamotrigine/topiramate	-/0	?	0/-	0
Lithium, valproate	++	0 (Valp) to + (Lith)	0/- (Lith.) to + (Valp)	0
Antipsychotics				
SGA*	++ (Quet)	0 (Arip.) to + (Quet, ris, oln.)	0 (Arip.)/ +(Quet, risp)/ +++ oln., clz.)	0 to + (if wt. gain)

-, reduction; 0, no effect; +, some effect; ++, moderate; +++, marked; ?, uncertain/variable

* though SGAs are often used in varying dose as an augmenting agent for depression, as mood stabilizers, or as sedative. †: used in impulsivity

Anti-adr.: Anti-adrenergic agent (e.g., propronalol), **Arip**: aripiprazole, **l/t:** lead to; **SGA:** second generation anti-psychotics, **Quet:** quetiapine, **Ris**: risperidone, **Oln**.-olanzapine, cloz.:clozapine); **Lith.**: Lithium; **SSRIs:** selective serotonin reuptake inhibitors; **SNRIs:** selective norepinephrine reuptake inhibitors; **TCAs:** tricyclic antidepressants; **Valp:** valproate; **Wt.:** weight

References: editors, Benjamin J. Sadock, Virginia A. Sadock. Kaplan & Sadock's Comprehensive Textbook of Psychiatry (Tenth edition). Philadelphia :Lippincott Williams & Wilkins, 2017.

Mazereel V, Detraux J, Vancampfort D, van Winkel R and De Hert M (2020) Impact of Psychotropic Medication Effects on Obesity and the Metabolic Syndrome in People With Serious Mental Illness. Front. Endocrinol. 11:573479. doi: 10.3389/fendo.2020.573479

II. Pre-operative Lifestyle Modification Programmes and Behavioural Interventions:

It seems prudent that multi-disciplinary team involved in care of person with obesity being considered for bariatric surgery to emphasize or work on with the patients on behavioural and LSMs. Such structured lifestyle programme can sensitise the patients about the need of benefit of maintaining a regular dietary and exercise regime apart from positive impact of a general wellbeing that such practices bring about both pre- and post-operatively.[28] It must be also highlighted here that mandatory putting a patient on LSMs programme before surgery or deeming it as an eligible criterion for surgery does not result in better pre- or post-surgical outcomes rather can lead to poorer outcome secondary to delay in getting the surgery, perceived stigma or feeling of being prejudiced, greater medical complications, etc.[29] Thus, the purpose of the LSMs should be to empower them, so that, a favourable lifestyle changes so developed could ensure maintenance of a good physical (diet, activity, etc.) and psychological wellbeing (motivation, self-efficacy, etc.) post-surgery.

III. Psychological interventions:

Psychological interventions are often indicated to address the psychosocial issues of patients being considered or have received surgery. Various evidence-based psychological interventions that improve post-surgical psychological and physical outcomes have been described below:

Pre-surgical psychological interventions:

Pre-surgical psychological interventions have been found to improve patients' surgical outcomes, including post-surgical physical and psychological adjustments. Pre-surgical non-pharmacological (and pharmacological interventions, when required) have been shown to improve both the physical (weight loss, physical activity) and psychosocial outcomes of the bariatric surgery, especially in the initial period, however, this improvement does not differ significantly after 1-2years (vs no psychological intervention pre-surgically).[30]

Brief supportive psychotherapy (BST) has been shown to improve post-surgical physical and psychological outcome of the individuals undergoing BS. For instance, Caniato et al. (2002) conducted an RCT involving at risk-individuals (with binge eating pattern, depression) undergoing laparoscopic adjustable gastric. Here, the intervention arm (n = 152) received *10 sessions of BST* aiming to address cyclical reaction pattern responsible for maintenance of a problem (binge eating pattern, depression, etc.) and focuses on changing the patient's perception of his or her experience rather than on altering the experience. While the control

arm received usual care *(*n=385). Participants were assessed on their weight loss and health status (objective parameters) and QoL and self-perception (Moorehead-Ardelt Quality of Life Questionnaire) both on short- (at 1yr) and long-term basis (>2yr). They found that those who received BST preoperatively had significantly higher weight loss (46% excess weight loss, EWL) at 1 year compared to those received usual care (40% EWL). A trend that followed on long-term basis as well, though this difference was not statistically significant. Furthermore, their QOL improved over time (both objectively and subjectively). The authors posited that preoperative BST gives a satisfactory result. They concluded that good compliance preoperatively corrected their eating habits that was maintained over years and was a good predictor of better long-term success[30]. Though better long-term data is still required.

A graphical depiction of pre-surgical psychological assessment and targeted intervention has been provided in Figure 1.

<pl insert figure 1 here>

Post-surgical interventions:

Likewise of the pre-surgical lifestyle and dietary modifications, post-surgical lifestyle and dietary modifications pay a huge dividend in long run, particularly those with history of BED or poor affective regulation.[29] The interventions should aim at promoting healthy eating pattern (chewing well, taking small bites, stop eating when first sense of the abdominal fullness appears, avoid in-between foods, not using food as a coping method for negative affective state, etc.) and regular physical activity (regular and scheduled exercise, etc.). These LSMs or behavioural interventions should also target various psycho-social aspects individuals who underwent bariatric surgery.[29,31]

The post-surgical phases have been categorized Post-surgical physical Adjustment (up to 6months post-surgery), post-surgical psychological adjustments (>6months through 18months), and long-term maintenance.[11] A graphical representation for the same post-surgical assessment and interventions have been shown in figure 2.

a. Post-surgical psychological interventions: Stigma and a strong sense of failure often prevent patients from seeking a MHP consultation promptly. Thus, depriving them of the necessary psychological support. It's interesting to know that as compared pre-surgical period, significantly greater proportion of the recipients of surgery expressed willingness to undergo post-surgical psychological sessions.[22] Literature also suggests that a regular visit to a

psychologist for behavioral interventions and CBT techniques (vs not following up in the such programs) results in greater improvement in various domains of MMPI. It needs to be highlighted here that although post-surgical psychological interventions do improve the physical health and mental health outcomes post-surgery, including coping skills for self-nurturance, on a short-term basis (1-2years), these improvements often do not persist beyond 2-3years.[32,33]

<pl insert figure 2 here>

Psychological intervention in the post-surgery physical Adjustment stage: This phase is also referred to as the honeymoon phase and is characterized by a rapid weight loss and elated mood. However, some individuals still face difficulties in making alterations in their patterns of eating and may experience food cravings, or anticipatory anxiety (regarding vomiting or plugging), among a variety of other issues. Interventions directed at correcting these problems can aid to adjust to the physical manifestations of surgery.[34,35] Similarly, desensitization and exposure and response prevention should be used as well as supportive therapy to allay their anxiety concerning the post-meal adverse physical problems and anxiety.

For instance, an RCT involving 17 participants (intervention arm vs 15 participants receiving minimal intervention (control arm)) who received behavioural intervention (monthly *behavioral consultations and biweekly weight management* materials for 6months) reported a significant improvement in postoperative physical and psychosocial functioning (family and marital life, activity) and eating behaviour (consuming less fat and protein) vis-à-vis' minimal intervention group. However, the difference was not significant in terms of post-surgical weight loss (both groups reported a significant weight loss at 1yr). Authors concluded that such behavioural interventions enhance post-surgical behavioural and lifestyle adjustments; though the findings were limited by the small sample size of the study. [36]

The Compulsive Eater's Program for Gastric Bypass Patients is another CBT -based program (where participants were provided with the reading materials, eating diary maintenance, forum to discuss their feelings, identifying and managing urges, self-esteem, change in body-image) [33]. A pre-post study design involving patients with full or subthreshold BED 2 to 6mth after surgery who were deliver CBT in group setting (participants met every week for 12weeks and subsequently, on monthly basis (in groups or individually) and assessed on Beck's depression inventory, binge eating disorder scale, Questionnaire on Eating and Weight Patterns, reported

the intervention had a positive impact on the patients' understanding and awareness of problems. It also helped them develop alternative coping strategies and means of self-nurturance. However, in the absence of the control arm the study findings need further exploration.

Although psychological interventions are promising strategies to address the psychosocial adjustments of the recipients of the surgery, including their adherence to the exercise regime and behvaioural modifications, it may not be logistically feasible to provide psychological assistance to all the patients, thus, at-risk individuals or those flagged in the pre-operative period should be regularly assessed (educating them about early signs/symptoms, this would facilitate early detection of psychological problems and prompt intervention) and, if required, provided with the regular sessions (CBT and inter-personal therapy style). Similarly, new role or relationship adjustments can also bring about significant stress for the patients as well as their family members; likewise, increased self-esteem and functioning may affect their family/marital dynamics. Thus, joint counseling would be helpful to address this issue.

Psychological intervention during the maintenance stage: The role of psychological interventions cannot be overemphasized at this stage. As the effect of the surgery wanes off after about 1-2years, the previous psychological problems (falling into the old pattern of eating, depression, low self-esteem, etc.) and new issues (loose-skins, cope up with the regain in weight, relationship issues, etc.) emerges. Therefore, psychological interventions aiming at correcting distorted cognitive patterns, poor coping methods, disillusionment, etc. would be useful.[37,37,38]

For instance, Kalarchian and Marcus (2003) highlighted that a "comprehensive" approach to treatment during this phase should focus on healthy eating habits, disordered eating patterns, and increased physical activity. Relapse prevention therapy targeting at high-risk situations (for maladaptive eating pattern, low-mood, stress, etc.) and a list of warning signs (missing follow-up visits, not complying with the dietary or exercise regime, reappearance of inter-personal issues, etc.) that serve to forewarn the individual that difficulties may lay ahead are also useful strategy.[31]

To summarise, psychological interventions are useful approach to manage the psychosocial problems among the recipients of surgery. Though the improvement is greatest initially post-adjustments periods (6m-2yrs post-surgery).

9. Recommendations

Based on the available literature and level of evidence, we recommend that individuals being assessed for bariatric surgery or prospective recipient of the surgery should undergo a formal psychological assessment by a psychiatrist. The assessment should have a decisive role on the surgery. It may include more detailed evaluation, need for regular monitoring, pharmacological or non-pharmacological intervention. Similarly, all patients who have undergone surgery should be evaluated post-surgery for their psychological adjustments, motivation to comply with the treatment regime, including life-style changes required, and evaluation pre-surgical psychological issues, if any (figure 2).

This CPG can help surgical team in a comprehensive assessment of the individuals being planned for the bariatric surgery. A proper psychological assessment can help in better post-surgical outcomes, both physical and psychological. However, this guideline can be tailored according to the needs of the Indian patients and the health infrastructure of the country. The detail recommendations have been elaborated in Table 6.

Table 6. Recommendation and clinical practice guideline pertaining to psychological assessment and interventions for individuals seeking bariatric surgery or recipients of bariatric surgery:

Domains of psychological evaluation and management	**Recommendations**
Structure of the multi-disciplinary team involved in bariatric surgery	Apart from surgeons, nutritionist, physical medicine expert, endocrinologist, nursing staff/counsellor, a MHP (a psychiatrist or psychologist) should be the part of the team. This would ensure a comprehensive assessment and care.
Participant's selection	Basic psychological assessment in all the individuals seeking bariatric surgery in a non-judgemental and non-stigmatized manner with the goal to identify at-risk individuals (flagging). More detailed structured interviews for individuals who are at risk of developing psychological problems after the surgery.

	To delay or refuse surgery for individuals who are actively suicidal, severely depressed, actively psychotic, ongoing substance use disorders, mental retardation, or dementia, etc.
Pre-surgical psychological assessment	A detailed semi-structured interview lasting for 30-45minutes. Use of interview schedule (like Boston or PsyBari schedule) Use of instruments validated in Indian population for assessment (Binge eating evaluation scale, PHQ-9, GAD-7, MMSE, MMPI, stress coping behavior scale or proactive coping inventory proactive coping, WHO-QOL-BREF, etc.) Assessing the level of motivation for the surgery and post-surgical recommendations (exercise, eating pattern, follow-ups) MHP should have decisive role in fitness for surgery based on the psychological status of the individual's seeking surgery.
Post-surgical psychological assessment	To assess the changed relationship, upcoming stressors, disillusionment, anticipatory anxiety, maladaptive coping skills, re-appearance of abnormal binge eating pattern, worsening of depression, sexual functioning, physical activity, etc.
Psychological interventions	*Pre-surgical:* Motivational interviewing to improve the motivation of the prospective recipients of surgery for taking non-surgical measures (adaptive eating pattern, exercise, stress management, etc.). Also, moderating the level of expectation from the surgery and potential roadblocks. Group therapy: psychoeducation about the surgery, mutual sharing of emotions, their attitude towards obesity and bariatric surgery, and learning from the experiences of others. Brief-strategy CBT. *Post-surgical:* CBT, behavioral interventions (for more adaptive eating patterns, regular exercises, stress management), relapse prevention strategies (cue-induced abnormal eating pattern), inter-personal therapy (to deal with the relationship issues), and family counseling. A multi-disciplinary comprehensive program when there are interrelated problems (psychological maladjustment, indulgence in old eating habits, non-adherence to exercise, and follow-ups).

Training	Psychiatry-trainees (including psychiatric nurses, psychologists, etc.) to be trained in MH aspects of obesity and bariatric surgery. Curriculum on bariatric surgery under the consultation-liaison programme Development and validation of psychological assessment and management protocol for Indian population seeking bariatric surgery. Research on the epidemiology and determinants of MH problems in those suffering from obesity and seeking BS. Further, culture-specific psychological interventions are feasible in the Indian health system.

BS: bariatric surgery; MH: mental health

Conclusion: Psychological problems are common among the obese individuals and those seeking bariatric surgery. Psychological problems are the result of the obesity rather than a cause for it. Bariatric surgery apart from bringing about an improvement in obesity and medical complications, results in improvement in psychological outcomes of the patients (such as depression, binge eating disorders, low-self-esteem, HRQoL, etc.). In contrast, pre-surgical mental illness does not predict post-surgical weight loss, though they worsen most-surgical functioning. Therefore, pre-, and post-surgical psychological interventions form an important part of medical care for individuals undergoing bariatric surgery. Psychological interventions (CBT, behavioural interventions, multi-model comprehensive program, etc.) improve in binge eating pattern, HRQoL, weight loss, however, these effects persist on short-to-medium term basis only. Mental health professionals have a major role to play in the decision-making for the surgery and medical care of individuals seeking bariatric surgery or recipients of surgery. This CPG adds to limited to the bariatric surgery and mental health from India. The guideline can help in developing protocol in psychological assessment and management of individuals seeking bariatric surgery. More research is required from India, particularly those pertain to the culture-specific interventions and tailored to health-infrastructure.

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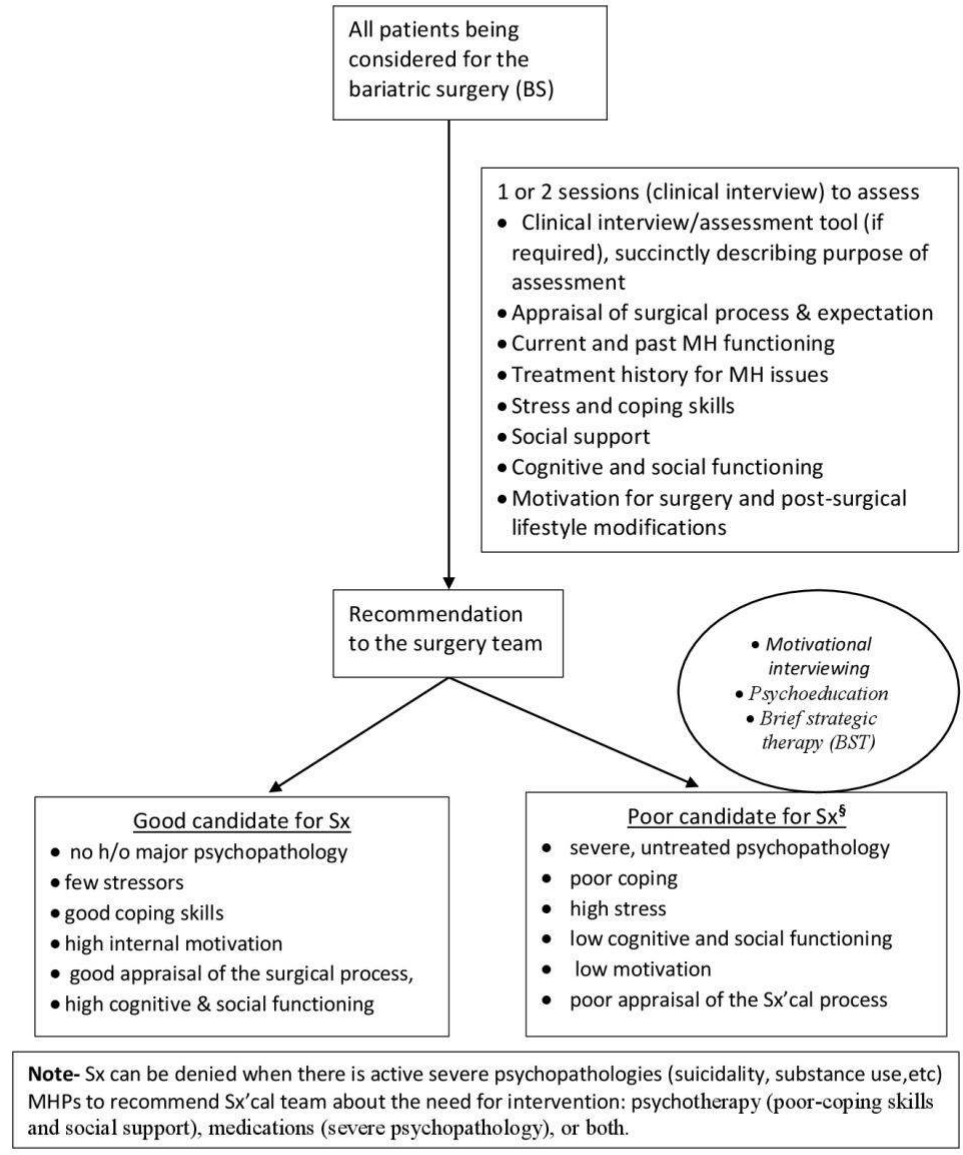
Figure 1. Flowchart depicting the pre-surgical assessment psychological assessment of the individuals undergoing bariatric surgery and potential intervention



§ it includes flagging of the prospective recipients of the surgery who require more closer monitoring/follow-up assessment; h/o: history of, FU: follow-up, MH: mental health, Sx: surgery

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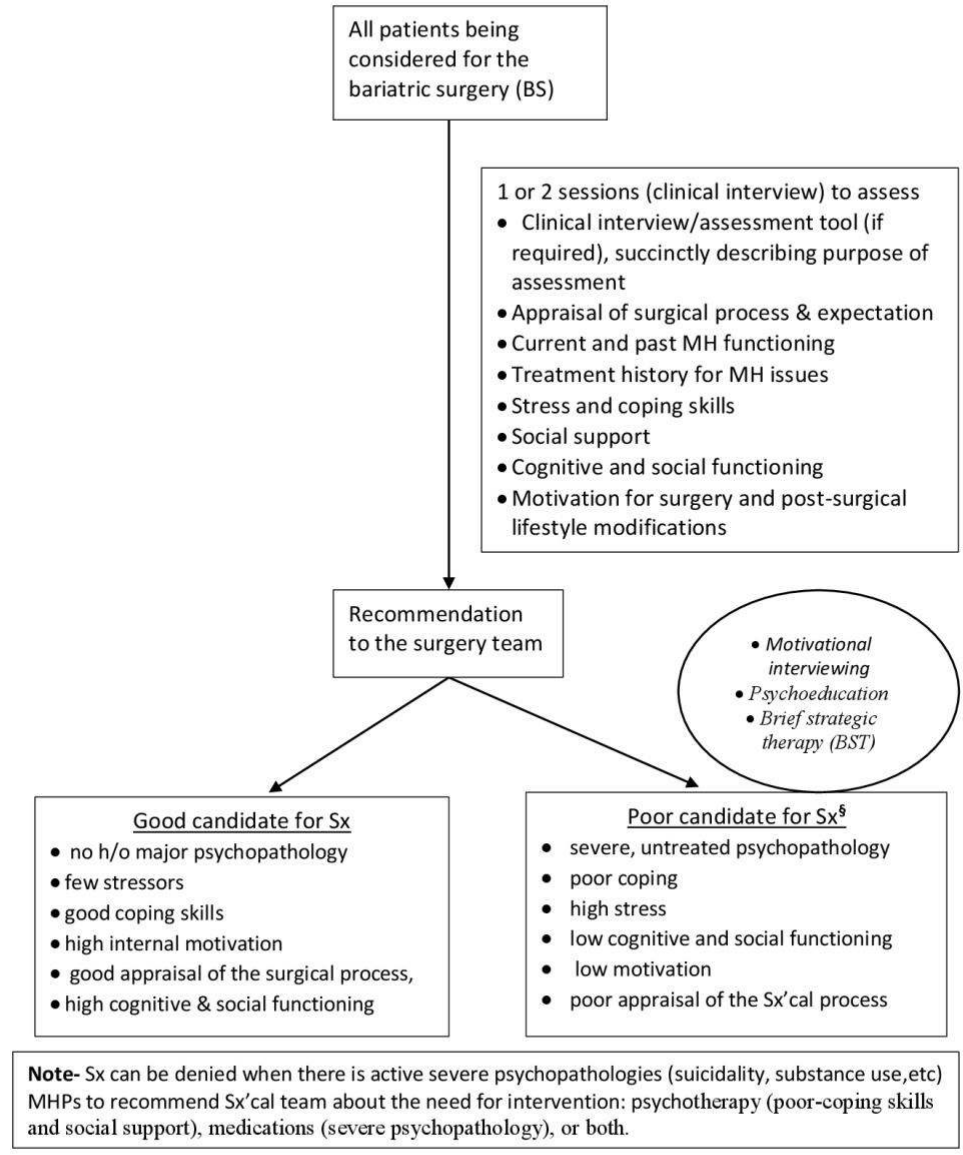

§ it includes flagging of the prospective recipients of the surgery who require more closer monitoring/follow-up assessment; h/o: history of, FU: follow-up, MH: mental health, Sx: surgery

Table 1. Prevalence of psychiatric disorders among the individuals seeking bariatric surgery

Psychiatric condition	Prevalence (pooled estimate†, 95% CI)
Any mood disorder	23 (15-31)
Depression	19 (14-25)
Binge eating disorder	17 (13-21)
Anxiety	12 (6-20)
Suicidal ideation or suicidality	9 (5-13)
Personality disorders	7 (1-16)
Substance abuse disorders§	3 (1-4)
Psychosis	1 (0-1)

† pooled estimate is based on random-effect meta-analysis, CI: confidence interval

§ **does not include nicotine dependence syndrome**

Adopted from (Dawes AJ, Maggard-Gibbons M, Maher AR, et al. Mental Health Conditions Among Patients Seeking and Undergoing Bariatric Surgery: A Meta-analysis. JAMA. 2016;315(2):150–163. doi:10.1001/jama.2015.18118**)**

Table 2. Components of pre-surgical psychological assessment

Succinctly describing the purpose of evaluation: allaying the misconception and prejudices related to psychological assessment (purpose to help the patient rather deeming them unfit)
Assessing knowledge and attitude: their understanding about the surgical procedure and its outcomes, including their level of expectation
Assessing current and past mental health functioning: assessing for all major psychiatric illnesses, particularly depression, BED, impulsivity, SUD, psychosis, personality ds. Etc. How symptoms were managed? (Types and setting of treatment) and their perception about the improvement with it.
Stress and Coping Skills: Level of perceived stress and mood in the last *6m-1yr* and their coping techniques (problem- vs emotion-focused) (particularly eating as a coping method). Their perception about upcoming stress (relationship issues, physical changes, etc.) and prospective coping strategies
Social support: level of social support they have and would need post-surgery towards treatment, including post-surgery follow-ups, and daily-life-related changes
Cognitive and Social Functioning: level of cognitive functioning (memory, attention, and concentration, comprehension [MMSE], planning, impulse control, motivation) and social skills (interpersonal skills, including communication with the treatment team, etc.)
Motivation: motivation towards surgery, reason to undergo surgery, locus of motivation (internal/external), comply with the recommendations, and behavioral changes required, etc.
Monitoring their compliance with the lifestyle modification: Monitoring their compliance with LSMs and factors (including psychosocial factors) influencing them
Objective Psychosocial Measures: Eating disorder (Binge Eating Scale, TFEQ), depression & anxiety (PHQ-9), personality (MMPI), QoL (WHO-QoL-Bref/ IWQOLLite)/ SF-36), coping skills (stress-coping behavior scale, proactive coping inventory)
Preparing a report to the surgical team: fitness for surgery, factors (risk and protective factors) influencing patients pre-and post-surgical adjustments, flagging*****, need for pre-or post-surgical non-pharmacological/ pharmacological interventions.

IWQOLLite: Impact of Weight on Quality-of-Life Questionnaire-Lite; *****Flagging refers to because of certain bio-psycho-social vulnerabilities patients should be observed more closely during the follow-up period); MMSE: mini-mental state examination, Minnesota multi-phasic personality inventory; SCBC & PCI are validated in Indian population; SF-36: symptoms checklist-36**;** TFEQ: Three-Factor Eating Questionnaire; WHO-quality of life-brief scale.

Table 3. Post-surgical psychological aspects of the individuals received bariatric surgery

Sexual functioning: usually post-operatively an improvement in sexual functioning of the patient is seen, however, it should be assessed for emergence of new symptoms.
Substance Use: Possible increase in substance use (including opioid analgesics) post-surgically, hence must be assessed routinely.
Psychosocial function and HR-QoL: an increase in marriage and new relationship; paradoxically, also, an increased rate of divorce/separation[#] also seen)
Neurocognitive functioning: Improvement, including in memory and executive function
Status of pre-surgical psychiatric problems/illnesses: Improvement in BED, depression, anxiety (though anticipatory anxiety[##] can emerge), self-harm, and suicidality, etc.
Re-emergence of psychiatric illness/symptoms: usually following 2-7years after the surgery (BED, depression, suicidality, etc.), including disillusionment (loose skin, etc.)
Change in the pharmacology of the psychotropic medications: the transit time of drugs may be increased following sleeve-gastrectomy (leading to greater or lesser absorption of medications) or altered rate of absorption post- RYGB surgery (Li, SSRIs, SNRIs, etc.).

[#] Due to leaving old unsuccessful and maladaptive marriage upon gaining self-esteem post-surgery; [##]after surgery secondary to dumping syndrome, etc.], AUC: area under the curve, resulting in differential effectiveness and toxicity; HR-Qol: health-related quality of life; SSRIs: selective serotonin reuptake inhibitor and SNRIs: serotonin-non-epinephrine reuptake inhibitors.

Table 4. Post-surgical psychological assessment of recipients of bariatric surgery

Perception of the patients about outcome of the surgery: Patients' perception about improvement in both physical (weight loss, eating pattern, etc.) and psychosocial (low mood, self-esteem, HRQoL, etc.) parameters following surgery, including level of satisfaction/dissatisfaction, and expected long-term outcome of surgery should be assessed.
Status of pre-surgical psychiatric illness: The status of pre-surgical psychiatric issues **(**depression, BED, Anxiety, personality issues, body-shape concerns, self-esteem, stigma, etc.) should be assessed.
Attitude and motivation towards post-surgical treatment: Their attitude and motivation for the demands of post-surgical treatment and LSMs needs to be assessed.
Dynamics of their relationship: The change in their relationship with spouse/partner and significant others and its influence on treatment adherence should be evaluated.
Upcoming stressors: Job-related changes and possible future stressors should be assessed.
Social support: Availability of current level of social support to meet the demands of treatment and daily life affairs should be assessed.
Coping methods: Their coping methods for any upcoming stressors should be evaluated.
Attitude and willingness to follow-up with the treating team: Their attitude and level of motivation to regularly meet the surgery team (including dietician, MHPs [particularly among those with pre-existing mental health concerns], etc.).

BED: binge eating disorders; HR-Qol: health-related quality of life; LSMs: lifestyle modifications, MHPs: mental health professionals

Table 5. Psychotropic medications and their propensity for weight gain, dyslipidaemia, diabetes mellitus, and hypertension

Drug class	Obesity	Dyslipidaemia	Diabetes	Hypertension
Antidepressants				
Bupropion	-	- (if l/t wt. loss)	?	+
SSRIs, SNRIs	?	?	-/0	0 (SSRIs)/+ (SNRI)
TCA, Mirtazapine, paroxetine	+	0 to + (if l/t wt. gain)	++ (TCAs)	+ (TCAs)
Anxiolytics				
Paroxetine, TCA, Mirtazapine	+	0 to + (if l/t wt. gain)	++ (TCAs)	++ (TCAs)
SSRIs, SNRIs	?	0	-/0	-/0
Buspirone, anti-adr., Benzodiazepines	0	0	0	0/ - (anti-adr.) 0
Pregabalin	?	?	?	?
Mood stabilizer†				
Lamotrigine/topiramate	-/0	?	0/-	0
Lithium, valproate	++	0 (Valp) to + (Lith)	0/- (Lith.) to + (Valp)	0
Antipsychotics				
SGA*	++ (Quet)	0 (Arip.) to + (Quet, ris, oln.)	0 (Arip.)/ +(Quet, risp)/ +++ oln., clz.)	0 to + (if wt. gain)

-, reduction; 0, no effect; +, some effect; ++, moderate; +++, marked; ?, uncertain/variable

* though SGAs are often used in varying dose as an augmenting agent for depression, as mood stabilizers, or as sedative. †: used in impulsivity

Anti-adr.: Anti-adrenergic agent (e.g., propronalol), **Arip**: aripiprazole, **l/t:** lead to; **SGA:** second generation anti-psychotics, **Quet:** quetiapine, **Ris**: risperidone, **Oln**.-olanzapine, cloz.:clozapine); **Lith.**: Lithium; **SSRIs:** selective serotonin reuptake inhibitors; **SNRIs:** selective norepinephrine reuptake inhibitors; **TCAs:** tricyclic antidepressants; **Valp:** valproate; **Wt.:** weight

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BS: bariatric surgery; MH: mental health

Management of Psychiatric Disorders with HIV and Dermatological Disorders

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PSYCHIATRIC ASPECTS OF HIV

Introduction:

Human immunodeficiency virus (HIV) infection is transmitted by three main routes: Sexual contact, through blood and from mother to child during pregnancy or breastfeeding. The immune deficiency results from decrease in $CD4^+$ T-cells resulting in reversal of normal CD4/CD8 T-cell ratio and dysregulation of B-cell antibody production. The stages of infection include acute infection, asymptomatic infection and acquired immunodeficiency syndrome (AIDS).

The relationship between HIV infection and psychiatric conditions is bidirectional. Those with psychiatric disorders like depression are more prone to contracting AIDS due to risky behavior including substance abuse. Similarly, those infected by HIV are more prone to develop psychiatric problems including depression and neurocognitive disorders. An Indian study found the lifetime prevalence of any psychiatric illness in persons with HIV to be 45%.[1] The common psychiatric and neurocognitive conditions associated with HIV along with their reported prevalence are enumerated in Table 1 [2]

Table 1 Psychiatric and Neurocognitive conditions associated with HIV

Psychiatric Disorder	Prevalence
Depression	**5.8-36**
Substance Abuse	**7-58.3**
Anxiety	**4.3- 44.4**
Psychosis	**6-17**
Adjustment Disorder	**3.8- 67.6**
Bipolar Disorder	**1.5**
HIV associated Neurocognitive Disorders	**43.9** **(ANI 26.2, MND 8.5, HAD 2.1)**
Delirium	**30-40**

Depression

Depression is the commonest psychiatric condition associated with HIV. The relation between HIV and depression is complex- depressed individuals may resort to risky behaviors like iv drug abuse which may predispose them to contract and transmit HIV. Depression is commoner in LGBTQ individuals and iv drug users who are more prone to contracting HIV. An individual who develops HIV may develop syndromal depression due to multiple reasons as mentioned in Box 1 [3]. Depression needs to be identified and treated promptly because it may interfere with adherence to HIV treatment. It also increases the risk of suicidal behavior. About 10% of HIV positive individuals die by suicide and about 20% resort to self-harm[3]. One Indian study reported 40% prevalence of depression among HIV positive patients out of which 14% harbored suicidal ideas.[1]

Box 1 Causes of depression in HIV

1. Chronic and life- threatening nature of the illness
2. HIV directly affects the subcortical structures that affect mood
3. Stigma and social isolation following the diagnosis
4. Antiretroviral and related drugs used in the treatment of HIV and its complications can cause depression- efavirenz, interferon, interleukin 2, steroids, zidovudine and vinblastine
5. Depression can be caused by opportunistic infections following HIV
6. Association with disease progression and depressive symptoms
7. Depression may occur in the earlier stages of HIV associated dementia
8. Elevated plasma pro-inflammatory cytokines

Assessment and management

Depression poses a diagnostic challenge in patients with HIV as it often presents with multiple somatic complaints rather than classical cognitive symptoms. Patient Health Questionnaire 9 is a useful screening tool for depression in these individuals. It is necessary to distinguish MDD from normal sadness, delirium, substance intoxication or withdrawal, opportunistic CNS infection (cryptococcal meningitis and toxoplasmosis) and dementia. Effect of drugs as mentioned in Box 1 needs to be ruled out.

Once the diagnosis of depression is confirmed, it needs to be treated promptly. Both Tricyclic antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs) have been found effective in treating depression associated with HIV. However, SSRIs are considered first line due to relatively better side effect profile. Fluoxetine, Paroxetine and Sertraline have been found effective in open label trials. Fluoxetine has also been found effective in a double blind placebo controlled study. Fluoxetine , paroxetine and sertraline have significant drug interactions with protease inhibitors and ritonavir. Hence, these agents should be used together with caution. Escitalopram and citalopram stand out as the safest SSRIs in terms of interaction with antiretrovirals. Testosterone has been found effective in treatment of depression in HIV patients with low testosterone levels. Stimulants like methylphenidate have also been found to be effective in treating depression, especially in those with overlapping symptoms of fatigue. Overall, treatment of HIV with antiretroviral regimen has also been found to improve depression to some extent.

HIV Associated Neurocognitive Disorder

HIV-associated neurocognitive disorder (HAND) is a broad term for the entire range of neurocognitive disorders induced by HIV. This ranges from asymptomatic neurocognitive impairment to HIV associated dementia (HAD).[4] Although the specific symptoms vary from person to person the entire cluster of symptoms are often described under the umbrella term of "AIDS Dementia Complex"(ADC). ADC typically occurs when CD4 cells count falls to less than 200 cells/µl. According to the Frascati criteria, HAND is classified into three categories based on increasing severity of impairment: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD).[4] The broad outlines of the Frascati criteria are mentioned in Box 2. The prevalence of HAND and its subtypes has been mentioned in Table 1. In an Indian study, 56% of the patients with advanced HIV were found to meet the criterion for impairment in two cognitive domains.[5] In another Indian study which examined neurocognitive deficits in early stages of HIV, seropositive patients performed poorly in digit symbol substitution test, trail making test and controlled word association test in comparison to normal controls.[6]

Box 2 Frascati Criteria

1. **Asymptomatic neurocognitive impairment:** Acquired impairment in cognitive functioning involving at least two of the following domains: Verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills. The condition does not interfere with everyday functioning and does not meet the criteria for delirium or dementia and there is no evidence of another pre-existing cause for it.
2. **Mild neurocognitive disorder:** Acquired impairment in cognitive functioning involving at least two domains as above. In addition, there is mild interference with everyday functioning (e.g. reduced mental acuity, inefficiency at work or homemaking, poor social functioning). It does not meet the criteria for delirium or dementia and there is no evidence of another preexisting cause for it
3. **Dementia:** Marked acquired impairment (2 SD below norms) in cognitive functioning involving at least two domains as above leading to marked interference with day-to-day functioning (work, home life, social activities). It does not meet the criteria for delirium and there is no evidence of another pre-existing cause of dementia.

Assessment and management

Some of the early indicators of HAND include deficits in psychomotor function (e.g. slowed movements, impaired coordination and gait), impaired performance on working memory tasks, mental agility (impaired performance on reaction time tests) and in mental flexibility. Episodic memory, particularly prospective memory, is most commonly affected. Language is often well preserved. Montreal Cognitive Assessment instrument can be used to assess cognitive deficits in HIV patients. A score of less than 26 necessitates referral for detailed neuropsychological evaluation. The Modified HIV Dementia Scale has been shown as a reliable and valid instrument for serial assessment of cognitive functions in HIV patients. Risk factors commonly associated with HAD are female sex, being elderly, higher HIV viral titers, lower socioeconomic group, substance abuse and iron-deficiency anemia.[7]

Well planned and optimized Highly Active Antiretroviral Therapy (HAART) regimen is the best possible method of managing HAND and lowering the risk of progression to HAD. There is no clear cut evidence regarding the superiority of agents with greater CNS penetration like abacavir. Stimulant medications like methylphenidate have shown benefit in some studies and no improvement in others. Physical activity may be an important measure for reducing HAND.[8]

Substance Misuse

Studies of HIV-positive individuals have found high prevalence levels of substance misuse (ranging between 7.0 and 58.3%). An Indian study reported the prevalence of substance dependence in HIV to be 10%. Substance abuse has been associated with poor adherence to antiretroviral treatment along with depression which further worsens the prognosis. The diagnosis of HIV often drives a person to substance abuse due to emotional issues and at the same time, intravenous drug use increases the risk of HIV. Opioid is commonly prescribed to persons with HIV but their illicit use is also common. Oral buprenorphine is commonly prescribed to HIV patients but they often use intravenous buprenorphine illicitly. Substance abuse of all types along with any other psychiatric comorbidity must be aggressively treated because it affects long term adherence to HAART and overall outcome in persons with HIV.

Anxiety Disorders

The prevalence of anxiety among HIV-positive individuals ranges from 4.3 to 44.4% (Table 1). An Indian study found the prevalence of anxiety among HIV positive individuals to be 36%. A diagnosis of HIV commonly triggers anxiety because the individual perceives this as a condition with no cure. This often begins before HIV test results are known and continues thereafter, irrespective of the result. Receiving notification of HIV-seropositive status can be a traumatic experience, it often leads to Post Traumatic Stress Disorder (PTSD) and suicide ideation. Anxiety can be a reaction to many stressful events that emerge during the course of HIV disease. Stress can be caused just after knowing HIV positive status , side effects arising out of treatment and adjustment to a completely new way of life. Stigma and fear of social isolation make HIV-positive individuals more vulnerable to anxiety.

Among the anxiety disorders, generalized anxiety disorder is the commonest. An Indian study found the prevalence of GAD in HIV positive individuals to be 12%. Just like depression, anxiety can adversely affect adherence to medication. It also leads to substance misuse. Anxiety regarding death due to the illness (death anxiety) is also common.

Among the treatment modalities, both pharmacological and psychosocial modalities have been found to be effective. Cognitive Behaviour Therapy and Cognitive Behavioural Stress Management (CBSM) have been found to be effective. SSRIs, manly fluoxetine, paroxetine and sertraline have been found to be effective in treating symptoms of anxiety in people with HIV. [9]

Adjustment Disorders

Adjustment disorder affects around 30% of individuals with HIV. Adjustment disorder can be with depressive or anxiety reaction or a combination of both. It occurs commonly at the time of diagnosis of HIV. Worsening of the medical disorders during the course of the illness may also give rise to adjustment disorders. Treatment of adjustment disorder is primarily based on cognitive-behavioral or supportive psychotherapy. Antidepressants, mainly SSRIs may also be used for short term.

Psychosis

The prevalence of new-onset psychosis among HIV-infected patients varies from 6-17%. The most common symptoms include persecutory, grandiose and somatic delusions. Hallucinations are less common. Impairment of attention and concentration and poverty of speech are also found in first episode psychosis in HIV patients. New-onset psychosis in HIV patients mainly develops in cases with advanced HIV infection and severe immunosuppression.[10] HIV patients with psychosis have higher mortality than those without which necessitates early treatment of such a condition. Risperidone has been found to be effective with minimal side effects in HIV patients with psychosis. One must be cautious about drug interactions with antiretrovirals. Risperidone, quetiapine and aripiprazole levels may be increased during concomitant administration with ritonavir and protease inhibitors due to inhibition of metabolism of CYP3A4 and CYP2D6. Efavirenz, nevirapine and zidovudine are known to cause psychosis-like manifestations as adverse effects.

Bipolar Disorder

Reported prevalence of bipolar disorder in HIV-positive individuals is 1.5%. Patients with bipolar mania may be at higher risk for HIV infection because of impulsivity, high-risk behavior like multiple unprotected sexual acts or intravenous drug abuse. Mania in later part of HIV infection may be associated with HAD.[11] Other causes of mania during the course of HIV could be due to side-effects of antiretroviral medications such as zidovudine and lamivudine, direct effects of HIV infection on the central nervous system , CNS opportunistic infections (e.g. toxoplasmosis, cryptococcal meningitis) and CNS tumours like non-Hodgkin's lymphoma. Manic episodes in HIV infected individuals need to be treated aggressively as the affected individuals may spread HIV infection to other people owing to their high libido and poor judgment. Sodium Valproate is the preferred mood stabilizer for treating mania in HIV patients. Liver function has to be monitored periodically. Lithium should be avoided because of chances of developing toxicity following HIV nephropathy. Likewise, carbamazepine is contraindicated because of increased chances of developing pancytopenia.

Personality Traits and Disorders

Patients with HIV have high prevalence of personality disorders. Compared to a general population rate of 10 %, the prevalence in HIV infected individuals is 19-36% and HIV at risk individuals is 15-20%. [12]The commonest type of personality encountered in these individuals is Antisocial Personality Disorder and the risk of substance abuse and high risk sexual behavior is significantly greater in this population. However, it is more convenient to assess the personality of HIV positive individuals along the dimensions of stable-unstable and introvert-extrovert not only to reduce stigma but also for the purpose of clinical utility.[12] Unstable extroverts are the

types which are most likely to engage in high risk behavior frequently leading to HIV infection and subsequent spread to others. They are the ones who are less likely to adhere to treatment and stick to advice of the clinician. Zuckerman Kuhlman Personality Questionnaire (ZKPQ) and NEO FFI are some of the instruments which may be useful in assessing persionality in these groups of patients. Some of the effective techniques in dealing with these individuals include focusing on thoughts and not emotions, behavioral contract, emphasizing constructive rewards, using relapse prevention techniques and coordinating with medical care services.

Delirium

Delirium occurs in approximately 30% to 40% of hospitalized AIDS patients.[2] Delirium in HIV patients is characterized by disturbance of attention and awareness along with disturbance in cognition which develops over a short period of time and tends to fluctuate in severity during the day. Patients with HAD and in advanced stages of HIV have the highest risk for developing delirium. Other general risk factors include advanced age, polypharmacy and medical problems. Delirium is often differentiated from other conditions because of a fluctuation in orientation and awareness and acute onset. The mainstay of management is finding out the cause and correcting it. Previously, common causes of delirium included atypical CNS and systemic bacterial infection with cytomegalovirus, mycobacterium avium, fungal infections, and hypoxia with pneumocystis carinii pneumonia. With the widespread use of HAART, delirium is more commonly associated with polypharmacy, HIV-related cerebrovascular disease, and psychoactive drug withdrawal or intoxication.

Delirium Rating Scale and the Memorial Delirium Assessment Scale are the preferred assessment tools. The diffuse cerebral dysfunction seen in delirium often causes slowing of EEG rhythms, and when present, may be helpful in supporting the diagnosis. Delirium in HIV/AIDS is managed by trying to find out the underlying cause and correcting it. Then attempt is made to reorient the patient through environmental cues. Pharmacotherapy may be initiated for symptomatic relief. The most favored antipsychotic has been low-dose haloperidol. Among the second-generation antipsychotics risperidone, quetiapine, and olanzapine are effective in resolving delirium symptoms.

Table 2 : Interaction between Psychotropic and Antiretroviral Drugs

Fluoxetine	**Level increased by protease inhibitors, decreased by nevirapine**
Paroxetine	**Level decreased by ritonavir, paroxetine increases ritonavir levels**
Sertraline	**Level increased by protease inhibitors, decreased by nevirapine**
TCAs	**Level increased by protease inhibitors**
Venlafaxine	**Level increased by protease inhibitors**

Aripiprazole	**Levels increased by protease inhibitors**
Clozapine	**Increased risk of myelosuppression with Zidovudine**
Quetiapine	**Levels increased by protease inhibitors**
All antipsychotics	**Increased QT_c prolongation with ritonavir, saquinavir**

Psychiatric management of Dermatological Disorders (Psychocutaneous disorders / Psychodermatological Disorders)

Introduction:

Disorders of brain and skin are closely linked to one another. Disorders of skin leading to change in looks and disfigurement can lead to various emotional problems. Similarly, various psychiatric issues can have dermatological signatures in the form of visible injuries or lesions. About 30% to 40% patients seeking dermatology consultation have an underlying psychiatric issue.

Classification:

The most widely accepted classification of psychocutaneous disorders is the one proposed by Koo and Lee.They categorized these disorders to mainly 3 types (1) psychophysiologic disorders, (2) primary psychocutaneous disorders and (3) secondary psychocutaneous disorders [13]

Table 1: Classification of psychocutaneous disorders proposed by Koo and Lee

Types of psychocutaneous disorders	Basis of symptoms production	Examples
1. Psychophysiologic disorders	Dermatological disorders which often flare up during periods of stress	alopecia areata, atopic dermatitis, acne, psoriasis, psychogenic purpura, rosacea, seborrheic dermatitis, urticaria
2. Primary psychocutaneous disorders	Psychiatric disorders are the root of developing dermatological conditions	skin picking disorder , trichotillomania, delusional parasitosis, body dysmorphic disorder, factitious dermatitis
3. Secondary psychocutaneous disorders	Patients develop psychological problems from chronic skin disease or disfigurement	Alopecia areata, cystic acne, hemangioma, psoriasis, vitiligo, ichthyosis, Kaposi's sarcoma

The classification also includes "cutaneous sensory disorders" which includes unpleasant skin sensations with no known dermatological cause but probable psychiatric etiology. Another category mentions psychotropic medications which may be helpful for management of dermatological conditions. For example, doxepin may be more helpful than standard dermatological agents for management of pruritus.

Recent Classification of Psychodermatological Disorders (Ferreira & Jafferany , 2021)[14]

Group A: Primary Psychodermatological Disease: Here, the primary dermatological disorders have a psychological mechanism, a psychological stress, and/or psychopathology as main elements in terms of either for induction or for worsening of the same. For example: psoriasis, alopecia areata, vitiligo, atopic dermatitis, chronic spontaneous urticaria.

Group B: Primary Psychodermatological Illness: In this group of dermatological conditions, there are skin symptoms, either with or without secondary self-induced skin lesions (such as excoriations), in the absence of a primary dermatosis. For example:

Psychogenic pruritus, delusional infestation, self-inflicted skin lesions, body dysmorphic disorder, dysesthesias like burning mouth syndrome, vulvodynia.

Group C: Secondary Psychodermatological Disorder: In this group, psychiatric complications of medications prescribed in dermatology and dermatological consequences of psychotropics are included:

-Secondary dermatologic disease related to psychiatric medications (Tables 2 and 3)

-Secondary psychiatric illness related to dermatologic medications. Common examples:

Depersonalization: minocycline

Mood disorders: isotretinoin; methotrexate; systemic steroids

Psychoses: dapsone; hydroxychloroquine

Sedation and drowsiness: antihistamines

Basic outlines of psychiatric assessment of dermatological patient

The basic approach to interviewing a patient referred from dermatology should follow some of the basic techniques as outlined in Box 1[15] For patients requiring psychodermatological evaluation, a liaison clinic comprising of a psychiatrist, a dermatologist, and a clinical psychologist is the most preferred set up. This is followed in Kasturba Medical College, Manipal in India[16]. However, due to dearth of specialists, such a composite set up may not be possible across the country.

Box 1- Basic Techniques for Psychiatric Assessment of Dermatological Patient

1. The patient should be asked to present an outline of the main reasons for the consultation, including treatment expectations
2. It is important to obtain a chronology and evolution of all symptoms including psychiatric problems
3. The fluctuation of psychiatric symptoms with remission and exacerbation of dermatological lesions should be specifically probed
4. Each psychiatric symptom should be assessed qualitatively- depression, anxiety, worry, obsession
5. Depression and suicide risk should always be explored
6. Stressful life events as well as chronic stressors must be probed
7. Attitude of self and others towards illness, specially stigma, should be explored
8. Secondary gain if any
9. Personality disorders

1. **Psychophysiological Disorders:**

Psychophysiological disorders are those dermatological conditions where psychological issues have a major influence in the course of the disorder. Stressful life events often cause flare ups of skin lesions. As many as 50% patients with acne and almost 100% patients with hyperhidrosis report emotional triggers.[17] An Indian study reported stressful life events in 26% of patients with psoriasis vulgaris and 16% of patients with chronic urticaria within 1 year preceding onset or exacerbation of the skin conditions.[18] Excessive workload, failure or poor performance in exam / interview, job loss, separation, break up of romantic relationship, or any kind of stress, anxiety, or other psychological issues generally precipitate or exaggerate dermatological disorders like psoriasis, atopic dermatitis, acne and hyperhidrosis.

Management:

- Identification of the stress factors is utmost important for controlling of these psychophysiological disorders.
- Stress management by lifestyle modification like time management, adequate sleep, balanced or healthy diet, yoga, meditation, deep breathing, deep muscle relaxation or other way of relaxation might help in managing stress and increase resilience.
- Pharmacological management with SSRIs and short course of Benzodiazepines has been beneficial when only non-pharmacological management is not helpful.

2. **Primary Psychiatric Disorders:**

This is the most important area where psychiatrist has primary role in management of psychocutaneous disorders. In this category the core problem is in psyche or brain which leads to dermatological disorders like skin picking disorder or any other body focus repetitive behaviors, delusional parasitosis, body dysmorphic disorder etc. A few important primary psychocutaneous disorders are –

2.1. Body-focused repetitive behaviors (BFRBs)

These are repetitive behaviors directed at the body in which patient is unable to control the act despite negative consequences. The salient features are:

- Repetitive self-grooming behavior like pulling, picking-scraping or biting own hair, skin, or nails
- Causes damage to the body area
- Multiple attempts to stop or decrease the behavior but failed
- Causes significant distress or impairment of functioning
- Disorder is not due to intake of substance or any other medical, dermatological or psychiatric disorders

Different conditions come under this umbrella term are as follows

- Hair pulling disorder (HPD) – Trichotillomania
- Skin picking disorder (SPD) – Dermatillomania / Skin excoriation
- Nail biting (Onychophagia) / nail picking (Onychotillomania)
- Tongue chewing
- Lip biting / cheek biting
- Nose picking

- **Epidemiology:**

Although epidemiological large studies are lacking, but there are a few small-scale studies of Skin picking disorder and Trichotillomania. It has been seen that about 3 % of general populations have any kind of BFRBs. Although in childhood both girls and boys are equally affected but in adolescent and adulthood women are affected much more than men (6 to 9 :1).[19]

- **Phenomenologically where do they fit in psychiatry?**

BFRBs have many features that may match with many psychiatric disorders. Although DSM5 describes the skin picking disorder (SPD) and hair pulling disorder (SPD) as obsessive compulsive and related disorders but there is still debate whether they are related to OCD or they fit into an independent category. ICD 11 has categorized these cluster of conditions as a separate category of BFRBs.

Management

- Interdisciplinary approach (dermatologist- psychiatrist liaison) is the key in managing this type of conditions.
- Diagnosis should be done after exclusion of other similar disorders
- As comorbidities are very high, psychiatrist should address the comorbidities like depression, anxiety, personality disorders for maximum benefits and reduction of relapse.
- BFRBs do not respond easily to treatment.

Psychological therapy:

Habit reversal training (HRT) and stimulus control are psychological treatment methods of choice for this group of disorders

- **Habit Reversal Therapy (HRT)** - Primary treatment for HPD and other BFRBs.

Here people learn how to recognize situations where they are likely to pull their hair and how to substitute other behaviors instead.

Components in HRT: Relaxation training is also an integral part of HRT

- Awareness training / self-monitoring – In this first 2 -3 sessions the person learns to recognize triggers and premonitory symptoms.

- Competence behavior – Replacing pulling, picking behavior with other adaptive behavior like, clench the fits to help stop the urge or redirect one's hand from hair to the ears in hair pulling disorder or squeezing a rubber ball in case of skin picking disorder.

- Generalization of behavior – Practising new learned skills in different situations

- **Stimulus Control –**

Modify environment to reduce opportunities to pull or pick. Generally, persons do the act while alone so they are advised to keep door open while doing work, persons cover their scalp with scarf, cap and wear gloves or strapping fingers so that they become unable to pull or pick.

- **Cognitive restructuring** – Cognitive therapy helps to identify and examine distorted beliefs people may have in relation to hair pulling, skin picking and replace those maladaptive thoughts with adaptive thoughts.

- **Acceptance and Commitment therapy (ACT)** – This helps to accept one's urges without acting on them. It is usually used as an adjunct to HRT/stimulus control

- **Drug treatment**:

  Several medications have been tried and showed significant results in HPD and SPD. The following medications can be used –

- **N-acetyl cysteine (NAC),** a glutamate modulator, has shown promising results for treatment of both HPD and SPD. N-acetylcysteine promotes the body's production of glutathione, a critical antioxidant and thus play a significant role in countering cellular inflammation. Based on evidences a trial of 1200-2400 mg/day NAC for at least three months is recommended as it is safe, well tolerated and effective in all severity levels.
- **SSRI / Clomipramine**- SSRIs are considered first-line treatment in BFRB though meta-analyses have not revealed significant benefits. Like OCD, the dose should be started low and have to go up to the higher therapeutic range. Clomipramine has been found to be effective in BFRBs specially in HPD.

- **Atypical Antipsychotics:** Olanzapine has been found effective in a meta-analysis of HPD treatments. Other antipsychotic agents, including haloperidol, risperidone, and aripiprazole, have also shown some benefit in uncontrolled studies.
- **Naltrexone** (opioid antagonist: 50mg / day)- Naltrexone reduces urges to engage in pleasurable behaviors. It is best for patients reporting strong urges to pull.

- **Lamotrigine** - It has been found effective in HPD and SPD in open label studies.

2.2. Delusional Parasitosis (DP): In delusional parasitosis, patients have a false, firm belief that they have been infested with parasites. It is also known as delusional infestation or Ekbom syndrome.

DP occurs as a single somatic delusion with no impairment of thought processes. Patients often complain of a sensation of bugs crawling on or inside the skin. Some even bring pieces of hair, skin or cloth in a matchbox as a proof of the existence of the parasites. This has been named as "matchbox sign". Patients may try to get rid of the parasites by using needles , fingernails and this often leads to bruises and excoriations.

DP can be classified as primary, secondary, and organic forms. In primary DP, the patient has the delusion of being infested with parasites without any other psychiatric or organic disorders. Secondary DP occurs secondary to other psychiatric disorders like schizophrenia, severe depression with psychotic symptoms and dementia. Organic DP occurs secondary to general medical conditions like hypothyroidism, anaemia, vitamin B12 deficiency, hepatitis, diabetes and HIV.

Treatment:

- Treatment strategies include pharmacotherapy as well as psychotherapeutic methods.
- A good doctor–patient therapeutic relationship is the key of effective treatment. Patient's belief should not be challenged in the initial encounter.
- Atypical antipsychotics (risperidone, olanzapine, amisulpride) are now recommended due to better response and favourable side-effect profile than first generation antipsychotics. Pimozide, which was classically used, has fallen out of favour due to cardiac side effects.

2.3 Body Dysmorphic Disorder (BDD): Prior to DSM5, BDD has been considered under somatoform disorder, but now in DSM5 it is included in OCRD group**.** Here the individual is preoccupied with one or more perceived defects or flaws in his or her physical appearance which the individual believes looks ugly, unattractive, abnormal or deformed. The defect does not seem to be a matter of concern for others. The individual usually performs repetitive behaviours like checking, grooming or reassurance seeking in response to concerns with appearance. BDD is associated with social anxiety, avoidance, depressed mood, perfectionism and low self-esteem. It can even lead to suicidality, especially in adolescents.[20]

The most common age of onset of BDD is ages 12-13 years with equal gender distribution. Most of the individuals consult dermatologists, cosmetic surgeons or maxillofacial surgeons to correct perceived defects in their appearance. Such interventions do not lead to improvement and often contribute to poorer outcome.

Management: BDD is chronic, but responds favourably to treatment However, initiating treatment may be difficult, as people with BDD may not believe that their excessive fixation on perceived flaws is a psychological disorder. An empathic understanding and establishment of a good therapeutic relationship is crucial in managing BDD.

- CBT is effective for treating BDD. The main step is cognitive restructuring by challenging irrational beliefs and perceptions regarding body features.
- SSRIs are the drug of choice in BDD. Clomipramine is another drug which has shown good results.

- SSRI combined with CBT produces favourable treatment outcomes

2.4. Psychogenic Pruritus: In this disorder, stress precipitates episodes of itching. Itching is often triggered by emotional cues, sometimes there is nocturnal variation also. There is localized or generalized chronic pruritus for greater than 6 weeks in the absence of an obvious somatic cause. Emotional stress causes itching, the patient scratches the affected area to obtain relief and further itch follows leading to a vicious cycle. Stress leads to release of histamine and other mediators of inflammation and also lowers "itch threshold". Psychogenic pruritus often occurs in cases of depression, anxiety disorders and alcohol abuse.
SSRIs and anxiolytics may help in reducing psychogenic pruritus. Habit reversal training is also effective in these patients.

2.5 Eating Disorders: Skin changes associated with eating disorders include gingivitis, lanugo hair, hyperpigmentation, cheilitis, melasma and brittle nails and hair among many others. The skin changes become more prominent when Body Mass Index becomes very low (usually less than 16 kg/m^2). CBT and antidepressants are the main treatment modalities.

2.6. Dermatitis artifacta (DA):
It is a kind of factitious disorder produced consciously by an individual to get attention from family members and physician. Common in women (female to male is 3 to 5: 1). Onset is in adolescent and early adulthood. Childhood trauma, abuse, dysfunctional family, borderline personality are some associated factors. Most commonly found in upper limbs, face and then other accessible areas. Pattern of lesions are dependent on the type of objects used and mechanism of injury and can include excoriations, superficial erosions, ulcers, abrasions, blisters, ecchymosis, purpura, erythema, edema, or signs of trauma and burns. Patients also may have multiple types of concurrent lesions and different stages of healing.

Management:
When DA is highly suspected, it is important to avoid unnecessary lengthy, time consuming, and costly tests, and better to focus on resolving the more probable underlying psychiatric issues. Initially, direct confrontation with the patient regarding mechanism of symptoms production and diagnosis is discouraged, as the patient may deny and will be lost for follow-up. A strong rapport with the patient is essential and it will take time to establish a therapeutic relationship. Underlying psychological issues need to be identified and gradual disclosure about the cause of this problem to the patient and family member need to be done. History of trauma, family issues, depression, anxiety, cluster B personality are common in these patients. Treatment should be personalized. No large studies about pharmacological management are there. A few case reports showed that SSRIs have some beneficial effects.

2.7. Dermatitis Para artefacta Syndrome: In this condition, patient seems to have lost control over manipulation of the skin. A minimal primary lesion is often characteristically excessively traumatized, leading to pronounced, serious clinical findings. Most common underlying psychiatric condition is impulse control disorder.

2.8. **Gardner–Diamond syndrome** (painful ecchymoses syndrome, psychogenic purpura, and painful bruising syndrome)
Usually seen in young women, it is characterized by periodically occurring painful infiltrated blue patches, multiple physical complaints, and characteristic psychiatric symptoms.
Clinical features: Initially there is itching, a feeling of tension, or burning pain, usually in the extremities and most often the legs. Then edematous erythematous plaques develop with ecchymoses, which heal within1–2 weeks. Characteristically, the course is of periodic episodes and healing without scarring. Systemic symptoms include episodes of abdominal pain, nausea, vomiting, diarrhea, weight loss, headache, blurred vision, paresthesias, and other neurological symptoms, as well as hematuria, hematemesis, metrorrhagias, and amenorrhea.
Psychiatric comorbidities: Dissociative disorders, anxiety and depression

2.9. Olfactory Reference Syndrome :

This disorder is characterized by persistent preoccupation with the belief that one is emitting a perceived foul or offensive body odor or breath, unnoticeable or only slightly noticeable to others. Olfactory Reference Disorder has been recognized as a distinct category in ICD 11. The affected individual repeatedly checks for smell, often tries to camouflage the smell in perfumes and often asks for reassurance from others. Treatment approach is the same as other OCRDs- high dose SSRIS or clomipramine along with CBT although trials specific to this disorder are lacking.

3. **Secondary psychocutaneous Disorder:** Chronic skin diseases, affecting exposed body areas, commonly lead to embarrassment, poor self-image, anxiety, depression, and even suicidal ideation. This is more common in the younger age group. Social impact is also huge. Often, they may have to face social isolation and discrimination and, at times, have difficulty getting jobs. Approximately 50 % of acne patients report emotional stress in close association with exacerbation of acne lesions. An Indian study found psychiatric morbidity in 35% of acne patients.[21] Studies have revealed a prevalence of depression in around 30% cases of alopecia areata. Another Indian study found psychiatric morbidity in 52% of patients with chronic dermatoses.

   Management:

- Generally, dermatologists refer these patients to psychiatrist when they find it difficult to keep them well without improvement of their psychiatric conditions.
- Treatment of dermatological disorders side by side management of psychiatric disorders to be done for optimum cure of these patients
- Identification of stress, anxiety, adjustment issues and management with proper counselling, psychotherapy including CT, BT, CBT is of helpful.
- Antidepressant like SSRI/ SNRI/Doxepin or hydroxyzine (if severe pruritus) are effective and short course of BZD may be helpful during bouts of severe anxiety
- Lifestyle modification and stress management are also essential

4. Cutaneous Sensory Disorders

Patients complain of abnormal skin sensations (itching, burning, pain) without the presence of primary skin lesions and a negative medical work up. These sensations can occur in any body region but tends to develop in areas with greater density of epidermal innervation, most commonly involving face, scalp, or perineum.[22]

Glossodynia

Patients with glossodynia present with chronic pain or burning sensations affecting the tip and sides of the tongue . There may also be changes in smell and taste. Glossodynia usually affects women in their 50s and is observed in over 5 percent of patients seen by dentists. The condition is usually idiopathic, but may result from vitamin B deficiencies, diabetes mellitus, candida infections, hormonal changes around menopause, and problems related to dentures or dental fillings. Higher rates of anxiety and depression are reported in patients with glossodynia.[22]

Vulvodynia

Vulvodynia is characterized by abnormal sensations in the vulvar region in the absence of skin lesions. The prevalence of vulvodynia is 15 percent in gynaecological outpatient practices. Most women with this disorder are between 20 and 50 years of age. They also have altered pain sensation in other parts of the body. There is growing consensus that vulvodynia is a chronic pain disorder. Vulvodynia patients experience more sexual dysfunction because of this discomfort. Amitriptyline, SSRIs, venlafaxine, gabapentin and pregabalin have been found to be effective treatments. CBT and biofeedback has also been found to be effective.

5. **Dermatological side effects of Psychiatric Drugs** -

Cutaneous lesions and various dermatological side effects of psychotropic medications are summarized in Table 2. Severe Cutaneous Adverse Reactions (SCAR) are potentially lethal events (10-30% mortality) that occur rarely (2-3 % of hospitalized patients) but in a sudden and unexpected manner. Various types of SCARs are Acute Generalized Exanthematous Pustulosis (AGEP), Stevens–Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS). [23] The basic identifying characteristics along with common psychotropics that may cause these reactions are summarized in Table 3. Psychiatrists should educate their patients and attendants regarding the possibilities of severe cutaneous reactions so that they are informed immediately and can take necessary measures including referral or hospitalization.

Table 2: Dermatological Adverse Effects of Psychotropic Medications

Drug	**Adverse Effects**

Lithium	Hair loss, scleroderma, vasculitis, acne, psoriasis
Valproic acid	Hair loss, Stevens–Johnson syndrome, toxic epidermal necrolysis, angioedema
Lamotrigine	Pruritic rash, hair loss, S–J syndrome, hypersensitivity reaction
Carbamazepine	Pruritic rash, S–J syndrome, hypersensitivity reaction
SSRIs	Allergic reaction (hives, urticaria), excessive sweating, pruritus; hair loss reported with fluoxetine
Venlafaxine	Erythroderma, erythema nodosum
TCAs	Photosensitivity, erythroderma
Phenothiazine	Erythema multiforme, S–J syndrome, drug hypersensitivity
Clozapine	Erythema multiforme, erythroderma
Alprazolam	Photosensitivity

Table 3: Severe Cutaneous Adverse Drug Reactions with Psychotropics

SJS/TEN	AGEP	DRESS
Carbamazepine, Valproate, Lamotrigine, Anxiolytics, Alprazolam	Carbamazepine, Valproate, lamotrigine,	Carbamazepine, Valproate, Lamotrigine, Olanzapine

Occurs in 4-28 days	Occurs in 1-11 days	Occurs in 2-6 weeks
Erythema, macular papules, urticaria, purpura or target rash, loose blisters that can fuse into bullae, causing skin epidermis to peel off	Joint, face, rash. Mainly aseptic pustule, less mucosal involvement, body temperature often >38 ℃	Measles-like rash with small pustules.In severe cases, erythroderma with extensive exfoliation of the skin, fever, enlarged lymph nodes
Death rate 25%	Death rate 5%	Death rate 10%

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Psychosexual health and sexual medicine in Consultation Liaison Psychiatry (CLP)

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1. INTRODUCTION

Sex and sexuality are the primal instincts of civilizations. They form the central core of social bonds, couple dynamics, relationships, intimacy and reproduction. It is a well-established fact that sexual expressions and manifestations are biopsychosocial constructs and have heavy bearing on cultural and ecological contexts. Classically, three dimensions of sexuality have been defined: desire, attachment and reproduction. Exploring these complex multi-dimensional interactions forms the basis of psychosexual health, which is in turn integral to sexual medicine. As defined by Masters and Johnsons in their classic Textbook of Sexual Medicine, sexual medicine is "that branch of medicine that focuses on the evaluation and treatment of sexual disorders, which have a high prevalence rate". Interestingly even though psychosexual disorders are predominantly dealt with by psychiatrists, their etiology may be multi-faceted including other medical comorbidities and iatrogenic causes, which brings us to the importance of consultation liaison psychiatrists (CLP) while dealing with sexuality and sexual concerns. It is not uncommon in clinical practice to routinely attribute sexual disorders and dysfunctions to a 'functional cause' thereby neglecting the emotional connotations, underlying distress, effect of medications and concurrent medical conditions. This can lead to misdiagnosis, underdiagnosis of these disorders, impaired sexuality and quality of life. With this background and with an aim to be a guiding outline for both psychiatrists and other medical specialties, these Clinical Practice Guidelines attempt to synthesize the role, evaluation, principles of assessment and management of psychosexual disorders in CLP settings.

2. USING THIS CPG: ROLE OF PSYCHIATRISTS IN TREATING SEXUAL DISORDERS IN CLP

CLP or Liaison psychiatry or consultative psychiatry is the branch of psychiatry that deals with the intersections between general medicine/surgery/pediatrics and psychiatry, usually taking place in a general hospital setting. This relatively developing branch has significant overlap with psychosomatic medicine (includes psychosexual disorders), pain management, health psychology and neuropsychiatry. The psychiatrist usually acts as an 'advising consultant' in response to specific requests/referrals from the other specialties. Now, when it concerns sexuality and related disorders, the concept of this discipline cannot be more stressed upon, "the interplay of biological and psychosocial factors in the development, course, and outcome of diseases." An ideal CLP service need to be a liaison-based model though mostly it's a consultation-based model that lacks inter-disciplinary discussion and further with significant heterogeneity in training and limited research, CLP is still a naïve field in India. This makes these CPG assume an increased importance.

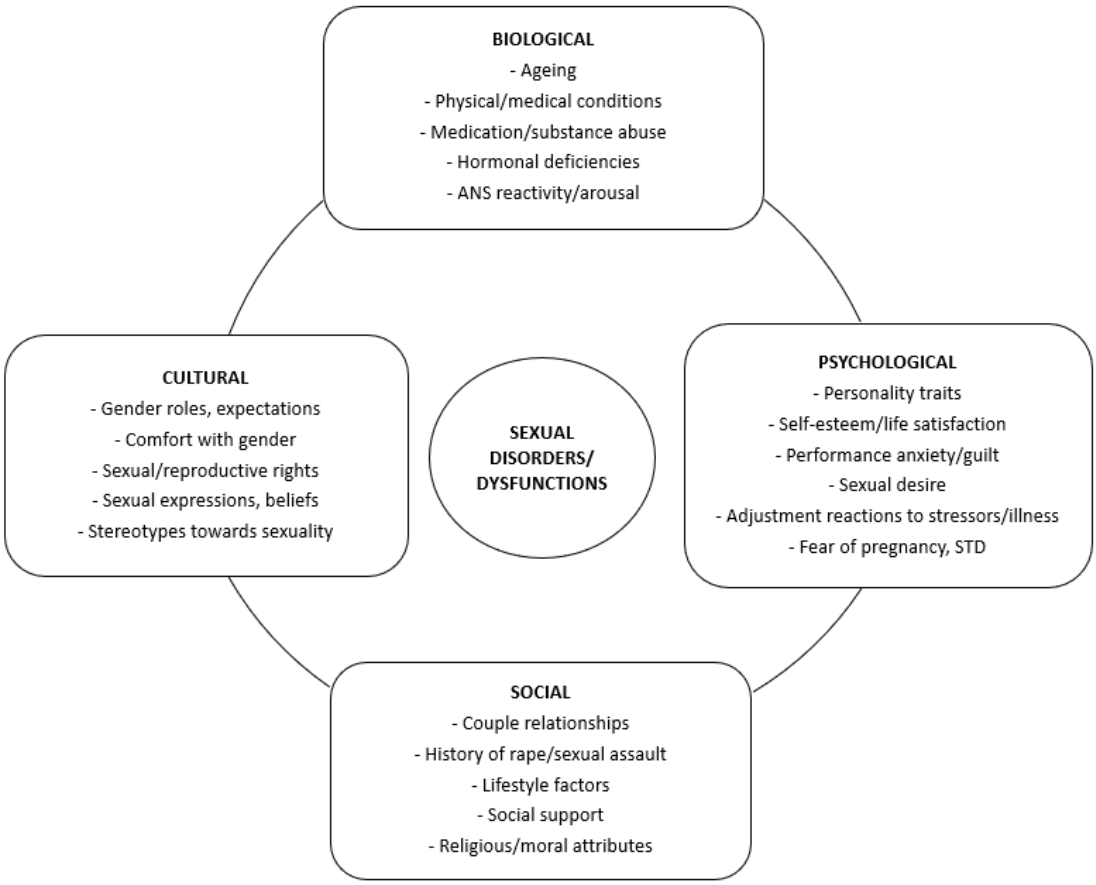
The Diagnostic and Statistical Manual (DSM)-5 prevents a sexual disorder to be considered as a psychiatric diagnosis, if the presumed etiology was a medical condition (or several concurrent medical conditions). In clinical reality however, there are no water-tight boundaries, for

example: an individual with adjustment issues related to a new diagnosis of malignancy can have resulting erectile dysfunction (ED), which can get further worsened by cancer chemotherapy. Hence it is a common practice for a physician to encounter a clinical context, in which a precise understanding of the specific cause of a sexual problem remain unidentified. Thus, even when a CLP referral is in place, it's the responsibility of the psychiatrist to recognize and determine the constellation of factors and possible causes that may impact the reported sexual disorders/dysfunctions. In fact, a host of medical conditions and medications can influence sexual functioning and responsiveness, which in turn is dependent on the existing sexual practices, sexual beliefs and other socio-cultural factors. These CPG are drafted to guide on clinical judgement to understand these complexities and enable the liaison psychiatrist to take a balanced and evidence-based decision on management of sexual disorders in medical settings. **Important to note, this paper does not deal with the general management principles of sexual dysfunction which are already covered earlier CPGs.**

3. SEXUAL DISORDERS AND DYSFUNCTIONS ASSOCIATED WITH GENERAL MEDICAL CONDITIONS

Even though the individual disorders are discussed subsequently, in this section we will outline the ways in which any chronic medical condition can influence sexual functioning and the principles of management. As mentioned before, the traditional duality of psychological and organic factors in sexuality is flawed and these two are inseparably combined. While on one hand coping style, personality traits, social support and external stressors can modulate inflammatory, immune, neurological and endocrine mechanisms, on the other hand any medical condition will have psychosocial offshoots that can disrupt physiology of sexuality. Sexual dysfunctions can be best understood through a biopsychosocial model **(Figure 1),** which is also relevant when apparently caused by medical illnesses as correction of the offending disease/medicine is often not enough on its own.

Figure 1: Biopsychosocial model of sexual disorders/dysfunctions



The two most common conditions causing this disruption are vascular erectile dysfunction (due to CAD, PVD, CCF, etc.) and dyspareunia due to vulvar vestibulitis syndrome. Based on DSM-5, the different types of sexual dysfunctions can be that of desire, arousal, orgasm and sexual pain. Broadly, the medical conditions that can lead to any or all of these conditions are enumerated in **Table 1.**

All sexual dysfunctions listed in the international classificatory systems can present to the consultation liaison psychiatrist (due to the medical condition or medications, and hence not primary in etiology). In order of frequency, they are:

Men:

- Erectile dysfunction
- Premature ejaculation
- Decreased libido and arousal disorders
- Anorgasmia
- Painful erection and ejaculation

Women:

- Anorgasmia and arousal disorders
- Reduced desire
- Reduced vaginal lubrication and vaginismus

- Other genital pain disorders

Table 1: Medical conditions associated with sexual disorders/dysfunctions

Group of disorders	Specific conditions
Cardio-vascular	• Atherosclerosis • Coronary Artery Disease / Angina • Heart failure • Hypertension • Peripheral vascular disease • Aortic aneurysms
Metabolic and endocrine	• Obesity • Dyslipidemia • Diabetes mellitus • Hyperthyroidism / hypothyroidism • Hyperprolactinemia / Hypoprolactinemia • Hypercalcemia • Cushing's Syndrome • Addison Disease • Sex steroid deficiencies
Neurological	• CVA • Dementia • Head injury / spinal cord injury • Multiple Sclerosis • Parkinsons Disease • Epilepsy
Malignancy	• Cancers of: Prostrate, testis, uterus, breast, ovarian (both direct and indirect) • All cancers: surgery, chemotherapy, radiation therapy, hormone therapy (indirect)
Others	• Chronic kidney disease • Connective tissue disorders / auto-immune conditions • Osteoarthritis / related musculoskeletal conditions causing chronic pain • Amputations • Urinary tract infections • STD and HIV • COPD / ILD

	• Cerebral Palsy • Medications (discussed separately)

Epidemiology

Data with regards to sexual dysfunction in medical conditions is complicated by methodological differences, use of heterogenous questionnaires and differing designs in population-based studies. Further, the usual dichotomy of 'psychiatric' and 'medical' etiology of sexual disorders used in many studies make epidemiological estimation difficult. Data from the National Health and Social Life Survey in the US showed that sexual dysfunction is more prevalent for women (43%) compared to men (31%). Also ageing, medication use, and presence of at least one comorbid medical condition increased the risk of problems related to arousal (in women) and erection (in men) by 1.5times, and this was independent of education and ethnicity. Several population-based surveys have shown that while erectile dysfunction (ED), premature ejaculation (PME), dyspareunia and hypoactive sexual desire were the commonest offshoots of general medical conditions, delayed ejaculation and frigidity were least prevalent. Besides, diabetic men develop impotence at least 10-15 years earlier than their non-diabetic counterparts. Based on guidelines, ED is a disorder in which it is fundamental to distinguish medical from psychological causes (or whichever is predominant) for understanding its prognosis and management.

Etiopathogenesis

There are several pathways through which medical disorders can lead to sexual disturbances. The exact manner or cause of a specific sexual disorder can have a plethora of explanations, which is beyond the scope of this CPG. Multi-factorial causation is a rule rather than exception and ageing, malnutrition, substance abuse, frailty and relationships are other influential factors. In general, urinary tract infections lead to arousal and pain problems in women and erectile issues in men. There are several mechanisms involved which are discussed eventually in individual sections.

In men, any condition affecting the ANS, local genital nerve supply, hormonal dysfunction and vascular regulation in response to arousal can affect the sexual cycle. One's inability to ejaculate can be the result of an interruption of the nerve supply to the genitals, which is often observed following traumatic surgical injury to the lumbar sympathetic ganglia, abdominoperitoneal surgery, or a lumber sympathectomy. Neurological disorders, prostatitis, and urethritis are possible causes of PME, though it rarely has a sole physical cause.

There are a variety of surgical/gynecological interventions like hysterectomy, ileostomy and mastectomy that can significantly affect body image and lead to women feeling less feminine and sexual. Also, decreased blood flow to the pelvic region following surgery involving the pelvic floor, abdomen, bladder, and genitals, or medical conditions like diabetes or atherosclerosis, can directly and indirectly impair sexual desire. There are a variety of medical conditions that can influence female orgasmic disorder including multiple sclerosis, pelvic nerve damage from radical hysterectomy or spinal cord injury. In the presence of vulvovaginal atrophy, with symptoms including vaginal pain, itching, or dryness, women are significantly more likely to have difficulty with orgasm compared to women without this disorder. Arthritis, diabetes mellitus, endothelial disease, thyroid dysfunction, urinary incontinence, inflammatory or irritable bowel disease (e.g., Crohn's disease, ulcerative colitis), and neurological disorders have all been identified to affect sexual interest and arousal in women. Comorbid medical disorder that impacts the pelvic floor or reproductive organs can lead to genito-pelvic pain/penetration disorders, with interstitial cystitis, constipation, vaginal infection, endometriosis, and irritable bowel disorder being common differentials to consider.
The various pathways in general medical conditions that can lead to disturbances in different domains of sexual cycle are detailed in **Tables 2 and 3**

Table 2: Sexual dysfunction associated with chronic diseases: The mechanisms involved (Adapted from Basson et al., 2010)

Type	Mechanisms	Examples
Indirect	Low mood	Associated with recent diagnosis of debilitating or terminal medical condition (strong link with ED and anorgasmia)
	Low energy levels	Fatigue can reduce sexual desire and motivation (in chemotherapy, infections, CCF, renal failure, etc.)
	Restricted mobility	Limited ability for physical intimacy, social touch, sexually stimulate partner/self, problems in sexual positioning and experimentation (Parkinson's and other motor disorders, ALS, CVA, brain and spinal cord injuries, post-amputation)
	Relationship dynamics	Couple discord, reduced social support, inability in finding a partner due to caregiver burnout, stress, perceived burdensomeness, lack of autonomy 'Medicalized lives' (recurrent dialysis, CKD, post-CABG, chemotherapy)
	Self-image disturbances	Disfiguring surgeries, scars, stomas, incontinence, muscle wasting, altered face and body movements in motor disorders (perceived lack of attraction)

	Infertility leading to perceived loss of sexuality	From surgical removal of uterus/gonads or chemotherapy or radiation therapy leading to gonadal failure
	Fear of sex	Fear of precipitating stress-induced medical event (CAD, CVA, genital pain in STD and surgeries, etc.)
Direct	Change in sexual desire	Due to hyperprolactinemia or anemia in CRF Due to testicular or ovarian failure after chemotherapy/hormonal therapy Narcotics causing gonadotrophin suppression
	Impaired genital response	Effect of disease: ED (multiple sclerosis, IPD, hypertension, CCF); orgasmic disorder (neurological conditions) Effect of surgery (radical prostatectomy, radical vulvectomy, etc.) Effect of radiation (vascular damage, vaginal stenosis, etc.) Effect of medications (ex: aromatase inhibitors, GnRH analogues leading to decreased genital sensitivity)
	Pain	Surgery/medication/radiotherapy leading to structural and chemical changes (ex: vaginal stenosis, reduced genital lubrication, etc.) Chronic pain from any condition leading to restriction of mobility and reduced sexual pleasure/altered orgasm

Table 3: Pathophysiology and types of sexual dysfunction in different medical conditions with their basic management principles

Disorder	Pathogenesis of sexual dysfunction	Management	Prevalence (%)*
Reduced sexual desire and arousal			
CAD/AMI	Low motivation for desire Fear of a subsequent attack Concern about using PDE5 inhibitors among those on nitrates Comorbid depression (almost in half of the cases)	Reassurance (risk is low and short-lived; RR is not increased in pre-existing CAD; regular testing) Need for regular exercise Use alternatives (trimetazidine) of nitrates Screen and treat depression/anxiety	15-20

CRF	Low testosterone in men (LH response blunted, GnRH pulsation reduced) Anovulation Hyperprolactinemia Anemia Uraemic menorrhagia/amenorrhoea Estrogen deficiency leading to dyspareunia	Limited benefit of testosterone supplementation (in men) Bromocriptine to reduce prolactin Vitamin D and zinc therapy Erythropoietin for anemia Cyclical progesterone for uremic menstrual irregularities Topical estrogen for genital pain	5-10
UTI and urinary incontinence	Reduced sexual motivation and orgasm	Postmenopausal estrogen therapy (limited benefit in those with infections) Surgical interventions for incontinence can worsen sexual dysfunction	5-15
Diabetes mellitus	Some correlation between high blood glucose and low desire Reduced serum testosterone and low GnRH pulses (in men) Reduced arousal, orgasm and genital pain (in women)	Adequate glycaemic control and screen for sexual problems	30-40 (more in older people)
Neurological conditions	Low desire with dopaminergic medications and in IPD, MS, etc. Hypothalamic lesions (CVA, head injury)	Correct the specific cause Non-pharmacological measures	15-70 (depends on the condition)
Adrenal diseases	Lack of sex androgens (DHEA)	Mild benefit of DHEA supplementation	No data
Primary and secondary hypogonadism in men, bilateral oophorectomy in women	Loss of sex hormones and sex hormone precursors affect processing and perpetuation of sexual stimuli Reduced availability of NO leading to ED	Treat causes of secondary hypogonadism Replace testosterone (prostrate or breast CA is a contraindication) Transdermal patch testosterone	10-20

		supplementation is of some benefit in surgical menopause	
Erectile dysfunction			
CAD	Endothelial dysfunction Structural atheromatous change Smooth muscle ischemic changes Venous occlusion	PDE-5 inhibitors (when not on nitrates) Vardenafil to be avoided in patients on class-IA anti-arrhythmics Apomorphine (D1/D2 agonist) can be tried when on nitrates Lifestyle modifications	35-50
CRF	Endothelial and cavernosal smooth muscle dysfunction Reduced NO production and NOS expression ANS dysfunction due to uraemia	PDE-5 inhibitors RAS antagonists and CCBs have an experimental role (not tested clinically)	20-25
UTI/BHP	Increased SNS, increased smooth muscle tone Reduced NOS activity in bladder outlet nerves Ischaemic smooth muscle fibrosis	Alfuzonsin is associated with least ED PDE-5 inhibitors + alpha-blockers have been tried (no RCTs)	15-20
CCF	Highest prevalence of ED (80-90%) Associated vascular risk factors and depression	PDE-5 inhibitors are useful and improve exercise tolerance Risk for hypotension	20-30
Diabetes mellitus	Reduced NOS activity (lack of NADPH, increased arginase) Increased smooth muscle contraction AGE products and ROS impair NO-induced vasodilation	PDE-5 inhibitors useful in 50% Intracavernosal PGE-1 in resistant cases	40-70
Hypertension	Endothelial dysfunction Vascular smooth muscle changes	CCBs and ARB improve endothelial functioning PDE-5 inhibitors are effective (vardenafil should not be used with alpha-blockers)	15-25

Primary and secondary hypogonadism	Low testosterone: reduced NO, low desire	Supplement testosterone if no contraindications Correct the secondary causes	60-80
OSA	ANS and endothelial dysfunction (nocturnal hypoxia and nocturnal SNS overactivity)	Sildenafil + CPAP improves ED in clinical trials	60-70
Neurological conditions	CNS, PNS, ANS dysfunction	PDE-5 inhibitors offer modest benefit (also in post-surgical cases) Intracavernosal PGE1 to be used in least possible doses	40-70 (depends on the condition)
Dysfunction of orgasm and ejaculation			
Infections (prostatitis, urethritis, epididymitis), PID	PME due to the local trigger Urethral strictures and ejaculatory duct obstruction Painful and low volume ejaculation Painful female orgasm	SSRIs (paroxetine has an advantage) CBT techniques Pubococcygeal muscle training Tamsulosin may benefit painful ejaculation Surgical treatment of strictures Postmenopausal estrogen and progesterone	20-30
Diabetes mellitus	Retrograde ejaculation Delayed/absent ejaculation/orgasm	Vibrostimulation Yohimbine, bupropion, buspirone, cyproheptadine can be tried Symphathomimetics can be used for fertility	30-40
Pelvic floor or local genital surgeries, Spinal Cord injuries	Absent/retrograde ejaculation (pelvic sympathetic nerve damage) Ejaculatory duct strictures Delayed orgasm Painful female orgasm	Mechanical stimulation Pelvic floor exercises Sympathomimetics for fertility Surgical correction may be necessary for incontinence	50-70

		Postmenopausal estrogen (for female orgasmic disorders)	
Endometriosis	Delayed/painful female orgasm	Bupropion/yohimbine has been tried Mechanical stimulation (vibrators) Treat underlying disorder	30-40
Pain disorders			
Peyronie's disease, phimosis, priapism	Pain on erection Difficulty in penetration Altered urinary frequency Unwanted painful erections	Mostly corrected surgically (rarely referred to a psychiatrist) Priapism can be a potential medical emergency Treat secondary causes	70-80
Dermatological disorders (in men)	Pain on sexual touch and penetration	Exclude STD Treat underlying disorder Couple counselling about non-penetrative and safe sex Psychosexual support (inability to contact a partner, disrupted self-image, lack of confidence, etc.)	No reliable data
Vulvovaginal atrophy	Introital pain during intercourse Post-coital burning Deep dyspareunia	Local estrogen therapy Tibolone is of benefit Dopaminergic drugs to reduce prolactin in pituitary disease Non-penetrative sex Surgery/radiation (for cancers)	20-30
Chronic abdominal pain conditions	Endometriosis, IBD, chronic PID, ovarian tumour, adhesions (deep dyspareunia and introital pain)	Pelvic floor exercises Treat specific conditions Address negative sexual experiences	30-40
LUTS and incontinence	Deep dyspareunia	Treat infections with antibiotics	No reliable data

	Post-coital burning (vulvar inflammation) Also associated with hypoactive sexual disorders	Surgical management of prolapse	
Pelvic radiation	Coital pain	Preventive measures (to be discussed with liaison) Couple counselling Topical estrogen, lubricants, vaginal inserts	40-50
Dysaesthetic vulvodynia	Introital dyspareunia	Topical estrogen/xylocaine EMG biofeedback CBT TCAs or AEDs for pain management Sexual counselling	No reliable data
STD	Superficial or deep dyspareunia	Follow STD management guidelines Protective measures for safe sex Deal with performance anxiety	Prevalence varies with the infection
Genital mutilation	Wide range of pain symptoms (Type I – III)	Sexual counselling, psychotherapy and support groups Involve sexual partner in decision-making Clarify legal/ethical responsibility Specific management of sexual dysfunction	

*Data is based on major epidemiological studies [National Health and Social Life Survey, US; American Diabetes Association; the National Cancer Institute; The American Cancer Society; Bureau of Health Statistics; Massachusetts Male Aging Study (MMAS); Framingham Heart Study]. The prevalence percentages are only tentative, can vary widely and should not be considered as strict cutoffs.

Evaluation and Management

As mentioned before, when sexual dysfunction is better explained by a medical condition, the individual cannot receive a psychiatric diagnosis as per DSM-5. In fact, a sexual dysfunction

diagnosis requires the treating clinician to rule out a multitude of problems that could be better explained by a nonsexual psychiatric disorder, by the direct and indirect effects of a specific substance, by a medical condition, or by marked interpersonal and psychosocial stress. **The usual protocol and outline of evaluation and management of sexual dysfunctions in both men and women have already been detailed in earlier CPGs and will not be discussed any further.** Here, we only consider the issues caused directly or indirectly by any medical conditions.

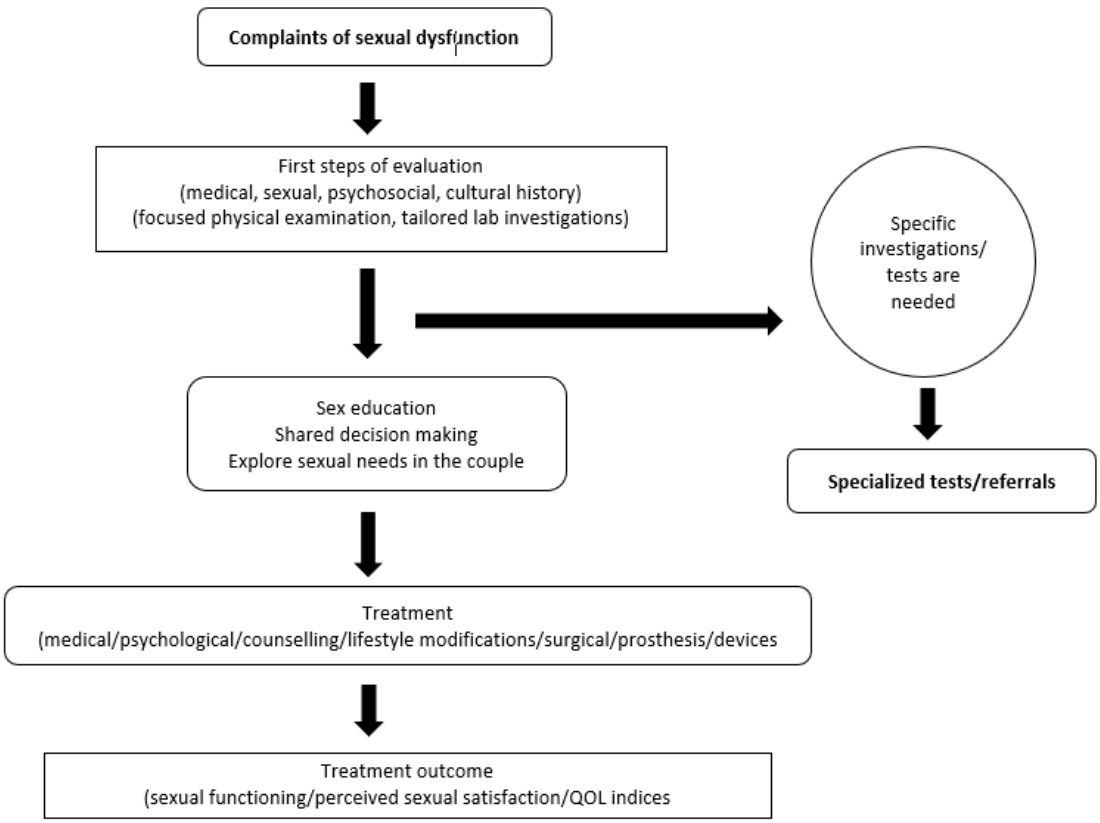
It is imperative that physicians are required to conduct a thorough evaluation of possible medical conditions that can lead to these symptoms, as many of these medical conditions are readily treated and can result in a reversal of symptomatology. Further, management in any such case starts with a detailed and comprehensive review of a patient's sexual, psychiatric and medical history including sexual practices, beliefs, myths and couple relationship dynamics. This needs to be supplemented with corroborative information from the partner, psychosocial assessment and comprehensive yet focused physical (and genito-pelvic) examination. Additional laboratory investigations are required as deemed necessary. Few salient principles are listed in **Table 5**. The key is often to have a multi-disciplinary bi-directional liaison with the respective specialty dealing with the medical condition and longitudinal follow-up.

An evidence-based management strategy for a CLP psychiatrist while evaluating a case of sexual dysfunction will be to have a holistic biopsychosocial plan incorporating the precipitating and perpetuating factors. This plan needs to be documented, backed up by relevant investigations and discussed with other clinicians involved in the care. A direct and constructive communication between all stakeholders is the key. It is essential to treat endocrinal abnormalities such as hypothyroidism, correct hormonal deficiencies such as low testosterone, and manage physically limiting disorders such as arthritis. To better differentiate between drug-induced SD and SD due to other causes, a baseline evaluation of sexual functioning is of utmost importance. Often it may be difficult to decipher the relationship between illness, medication, and SD since the underlying illness for example cardiovascular disease may itself be associated with SD.

At times, the burden of chronic illness, adjustment issues and self-perceptions related to it may impair sexual relationships which need to be addressed. The offending medicine leading to sexual dysfunction needs to be halted and is the most definitive treatment in some cases. While it is important to consider that there is no threshold or optimum level of sexuality, the perceptions and needs of the individual/couple in question are vital and will guide treatment decisions. Sexuality also involves closeness, intimacy, emotional bonds, and social touch and equating it with intercourse is reductionistic. Keeping the individualised sexual needs and changing descriptions of intimacy with ageing are necessary for the treating psychiatrist.

The basic steps for assessing and treating sexual dysfunction (International Consultation on Sexual Medicine ICSM-5) which also need to be followed in the CLP setting are depicted in **Figure 2**.

Figure 2: International Consultation on Sexual Medicine (ICSM-5) guidelines for evaluating sexual dysfunction (adapted from Montorsi et al., 2010)



Besides treating the medical cause of sexual dysfunction, it might necessitate biological treatments like oral medications (phosphodiestrase-5 inhibitors, non PDE-5 agents, antidepressants, hormones), injections, devices, implants, etc. as well as psychosocial interventions (individual psychotherapy, couple therapy, and sex therapy). The non-pharmacological techniques are extremely important but often neglected. They do not exist in vacuum and are usually coupled with sex education, clarifying the myths related to sexuality as well as anxiety related to the concurrent medical illness **(Table 5).** The guidelines for these treatments are not much different from sexual dysfunction without a medical cause and hence will not be discussed in detail. While some strategies are mentioned in **Table 4**, other relevant management techniques will be detailed in subsequent sections under specific disorders.

Table 4: General areas of assessment/evaluation in sexual dysfunctions induced by medical conditions

• Past psychiatric and medical history • Premorbid personality • Sexual attitudes and beliefs

- Current medical state (cardiac, respiratory, genito-urinary, metabolic, neurological)
- Mobility, pain and continence status (for sexual activities)
- Pre-illness sexual behaviour (preferences, frequency, fetishes)
- Detailed review of current medications and their impact on sexual cycle (whether change of medicines had an influence on sexuality)
- Duration, type and context of the sexual dysfunctions; treatment received (pharmacological and psychosocial)
- Specifics needed for the dysfunctions:
  - Motivation/fear/apprehension about sex
  - Perceived sexual satisfaction/pleasure
  - Morning erections
  - Masturbatory practices
  - Distracting/anxiety-provoking thoughts during sex
  - Experiences of orgasm/intercourse
  - Ask about vaginal lubrication, coital pain and post-coital dysuria
  - Ask about male dyspareunia
- Couple relationship status, quality and communication
- Independence and autonomy for sex in daily living
- Effect of medical illness on sexual self-image and body satisfaction
- Detailed physical examination (including local genital evaluation): especially in cases of ED, pain disorders, problems with arousal, neurological conditions)
- Mental status examination (depression, performance anxiety, stressors)
- Blood investigations (to rule out anaemia, dyslipedemia, hypo/hyperthyroidism, hypogonadism, hyperprolactinemia, sex steroids/androgens)
- ECG and ECHO for cardiac status
- Penile Doppler / Plethysmography (rarely needed)

Investigations

Basic:

- CBC
- Fasting Lipid Profile
- Metabolic panel and blood sugars
- RFT, TFT, LFT
- Urine analysis (routine and culture), drug screen
- Hormonal assays[1]

Specific disorders[2]:

- ED: Blood (Total and free testosterone, LH, serum prolactin), vascular testing (duplex ultrasound, cavernosometry, nocturnal penile tumescence, SEP)
- Female sexual arousal disorder: Vaginal photoplethysmography (to test blood flow and temperature, biomechanical function of female genital tract, testing vaginal pH

• PME: ejaculatory latency testing (rarely used in real world setting)
Certain hormonal levels (standard)[3]: • LH: 5 – 15 mIU/mL • FSH: 5 – 15 mIU/mL • Prolactin: < 15 mIU/mL • Total testosterone[4]: 300 – 1000 ng/dL (adult males), 30 – 120 ng/dL (adult females) • Free testosterone[4]: 5 – 21 ng/dL (adult males), 0.3 – 0.85 ng/dL (adult females) • SHBG: 0.6 – 3.5 mg/L (adult males), 2.5 – 5.4 mg/L (adult non-pregnant females)

[1]Normal ranges and standardization vary

[2]For PME (males) and orgasmic disorder (females), self-report is always the best diagnostic marker

[3]Hormonal levels can highly fluctuate based on medical conditions, psychological factors, diet, sexual activity, etc.

[4]Blood for serum testosterone assessment need to be drawn from 8 – 10am and not during early follicular phase in pre-menopausal women

Table 5: Factors involved in psychosocial management

• Reassurance and sex education • Address barriers in seeking treatment (misinformation, stigma, fear of judgement and embarrassment) • Lifestyle measures (exercise, Yoga, optimum control of vascular risk factors, nutrition, weight management, tobacco cessation, alcohol restriction) • Treat the apprehensive anxiety of recurrence following AMI/CVA • Encourage self-stimulatory activities for single individuals • Link sexuality with intimacy and emotional closeness • Address associated somatic complaints and depression/performance anxiety • Positive self-talk and positive attitudes towards sex/genitals
Specific interventions: • Pelvic floor exercises, vaginal containment, suitable intercourse positions and progressive muscle relaxation (for dyspareunia) • Sensate focus, stop & start technique, squeeze technique (for PME) • Couple and sex therapy (with homework assignments) • Mindfulness-based group therapy • CBT • Tailored psychosocial interventions that target coping style and illness perception modification (in cancers, genital surgeries, etc.) • Cognitive/behavioural interventions for sexual minorities (especially those on HRT)

4. SEXUAL PROBLEMS IN NEUROLOGICAL DISORDERS

The following table **(Table 6)** provides an overview of the etiologies, management and prevalence of sexual difficulties for pertinent neurological illnesses. General measures for all illnesses include proper education, addressing partner concerns, evaluating beliefs about sexuality and sexual health, dispelling myths and misconceptions, symptomatic management of associated complaints and removal or modification of any offending pharmacological agent with a propensity to cause sexual dysfunction.

Table 6: Sexual difficulties in neurological diseases

	Neurological condition	Etiology of sexual difficulties	Management of sexual difficulties	Prevalence
	Neurocognitive disorders	1. Loss of roles, loss of employment, financial constraints, increasing dependence, fatigue, caregiver burden, social isolation, and the knowledge that the person may soon lose the ability to connect with their loved ones. 2. Impact of the disease, the loss of self-concept, and feelings of anger and disappointment aimed toward themselves and their partners.	1. Hormone replacement 2. Phosphodiesterase inhibitors, and vaginal creams or lubricants. 3. Sexual assistive devices 4. Provision of physical intimacy and privacy in Long-term residential facilities Management of inappropriate sexual behavior **Environmental** 1. Combating under-stimulation, involvement in daily activities. 2. Comfortable clothing that cannot be easily shed.	Men: ED (40-60) Women: Reduced libido (40-50) • More than half of individuals living with AD have comorbid ED due to vascular pathology • 30-40% inappropriate sexual behaviors in FTD

		3. Deficits in executive functions. 4. Obstruction by physical symptoms such as problems with vision, hearing, or fine motor skills, physiological difficulties with arousal mechanisms, and psychological lack of desire or sexual awkwardness.	3. Providing soft toys and aids. 4. Separating the patient from the individual towards whom the sexual behavior is directed. **Pharmacological** 1. Antidepressants-Paroxetine, Citalopram, Mirtazapine, and Trazodone. 2. Antipsychotics- Haloperidol, Risperidone, and Quetiapine to reduce the frequency of acting out behavior. 3. Anticonvulsants such as benzodiazepines, Carbamazepine, Valproate, Gabapentin, and Topiramate 4. Anti-dementia treatments such as Donepezil and Memantine 5. Anti-androgens- Medroxyprogesterone acetate, Ethinylestradiol, Finasteride, Ketoconazole, Spironolactone, and Cimetidine.	
	Idiopathic Parkinson's Disease	1. Motor symptoms: bradykinesia, rigidity, resting tremors, akinesia, and loss of fine motor skills may hamper one's ability to	1. Adequate control of tremors, akinesia. 2. Anticholinergic agents for sialorrhea	Men: ED, PME, decreased libido (50-80) Women:

		participate in sexual activity. 2. Muscle rigidity and akinesia may also worsen at night due to dose scheduling 3. Nonmotor symptoms: anxiety, depression, cognitive impairment as well as autonomic disturbances affecting the bowel and bladder 4. Decreased Dopamine levels in the brains and reward circuitries of these patients (reduced 'hedonic' pleasure)	3. Ephedrine, Midodrine for orthostatic hypotension 4. Sexual difficulties- Sildenafil, Apomorphine, and PGE1for ED. 5. Vaginal lubricants, topical creams. 6. DBS of the subthalamic nucleus for ED 7. Treatment of hypersexual behavior-Antipsychotic agents like Quetiapine.	Arousal disorders, vaginal tightness, reduced libido (30-50)
	Stroke	1. Sexual activity may be impacted by muscular weakness, stiffness, fatigue, pain, altered sensations, impaired mobility, and incontinence. 2. Depression and anxiety after stroke 3. Patients and partners may also avoid sexual intercourse for fear of precipitating another stroke.	1. Physiotherapy 2. Rehabilitative aids. 3. Speech therapy 4. Management of incontinence Management of uncontrolled diabetes 5. Sildenafil for ED 6. Baclofen, Tizanidine for spasticity 7. Measures as enlisted above for hypersexual behavior	Men (50-70) Women (20-35) [one-third within six months of stroke]

	Epilepsy	1. Epileptiform discharges may disrupt pathways in the limbic system which play an important role in human sexual behaviors. 2. Poor self-esteem and fears of rejection may lead to avoidance of sexual contact. 3. Hyperventilation is known to provoke epileptic seizures and commonly accompanies sexual activity. 4. Temporal lobe epilepsy (TLE) is associated with sexual auras, ictal orgasms, and sexual automatisms and thus this subtype may have a larger impact on sexual functioning.	1. Choosing Antiepileptic agents that are neutral to the P450 enzyme system and that have a lesser propensity to alter sex hormone-binding globulin (SHBG). 2. Hormone replacement in both sexes 3. Evaluation and management of endocrinological disturbances such as hypogonadotropic hypogonadism, hypothalamic dysfunction, and PCOS.	Men: ED (40-50) Women: diminished libido, arousal and orgasmic ability (10-20)
	Multiple Sclerosis	1. Direct compromise of the spinal cord 2. Involvement of the bowel, bladder, and lower limbs 3. Spasticity and ambulation difficulties 4. Insults to self-esteem and sexual expressivity, depression	1. Sildenafil and PGE1 for ED 2. Sildenafil for Vaginal lubrication 3. Baclofen, Tizanidine, botulinum toxin for Spasticity 4. Address comorbid depression, anxiety, and bowel and bladder difficulties.	Men: ED (50-60) Ejaculatory and arousal disorders (30-40) Women: Arousal disorders (20-30)

	Head injury	1. TBI can lead to physical disability, cognitive impairment, and personality changes 2. Hypersexual behavior may be associated with lesions in basal frontal and limbic areas. 3. Pituitary damage and medication may also compound the sexual difficulties after TBI. 4. Depression	1. Baclofen, Tizanidine, botulinum toxin for spasticity 2. Dopamine agonists such as Bromocriptine to improve motivation, apathy 3. Atypical antipsychotic medication, MDPA, SSRIs for sexually disinhibited behavior 4. Sex therapy and behavioral approaches such as time out, social skills training, self-monitoring for sexual urges, and feedback may be employed for inappropriate sexual behavior. 5. Addressing physical limitations and bowel or bladder incontinence and provision of suitable aids. 6. Pituitary damage should be screened for at 3 and 12 months after head injury.	40-60 (both genders)

	Spinal cord Injury	1. Chronic pain occurs in about one-third of cases 2. Bladder and bowel urgency and incontinence. 3. Limitation in movement, motor control, and sensory abilities. 4. Decreased vaginal lubrication and pain during intercourse related to the level and completeness of the lesion. 5. Injuries to the sacral segments and the cauda equine impair reflex activity and reflex erections. Lesions above T10 substantially impair the capacity for psychogenic erections. 6. Women with S2-S5 spinal segment injuries are less likely to experience orgasms.	1. Sildenafil, PGE1 for ED 2. Tadalafil, Vardenafil, Midodrine for Ejaculatory dysfunction as adjuncts to PVS 3. Sildenafil for lubrication 4. Baclofen, Tizanidine, botox for spasticity 5. Audiovisual stimulation leads to subjective and autonomic responses similar to healthy controls in women. 6. Methods focused on partner satisfaction, nonsexual forms of intimacy and manual stimulation.	Men: 40-50 Women: 5-15

Abbreviations used:
BPSD- Behavioral and Psychological Symptoms of Dementia
DBS- Deep Brain Stimulation
ED- Erectile dysfunction

MDPA- Medroxyprogesterone acetate
PGE1- Prostaglandin E1
PVS- Penile vibrostimulation
SSRI- Selective serotonin reuptake inhibitors
ED- erectile dysfunction
PME – premature ejaculation
AD-Alzheimer's Disease

5. NON-PSYCHOTROPIC MEDICATION-INDUCED SEXUAL DYSFUNCTION

Sexual dysfunction (SD) may be caused by a variety of medical conditions and their treatments. The commonly implicated agents are psychotropic medications such as antidepressants and antipsychotics. However, antihypertensives, antacids, and contraceptives, among others may also be linked with sexual difficulties. Understanding the potential for drug-induced sexual problems and their negative impact on treatment adherence can better enable clinicians to tailor treatment strategies for the patient and their partner.

Classes of non-psychotropic medicines linked with SD have been enlisted in Table 7.

Table 7: Classes of non-psychotropic medication and their sexual side effects

S.no.	Class of drugs	Drug names/subsections	Sexual side effects
1.	Antihypertensives		Decreased sexual desire
		Beta blockers: Atenolol, Acebutolol	Decreased libido, ED, decreased subjective and physiological arousal.
		Calcium channel blockers	Decreased libido ED
		Amlodipine,	Decreased libido
		Nifedipine	Gynecomastia, ED
		Diltiazem	ED, decreased libido
		Verapamil	Vaginitis, decreased libido, non-specific sexual difficulties
		Diuretics	
		Spironolactone	
		Thiazide diuretics (Chlorthalidone)	
		ACE inhibitors:	
		Enalapril, Lisinopril, Perindopril, Benazepril, Trandolapril	Decreased libido, ED

		Angiotensin receptor blockers Irbesartan (NOTE: Valsartan and Losartan may improve sexual functioning in hypertensive males)	
2.	Alpha adrenergic blockers	Clonidine Prazosin, Tamsulosin, Doxazosin, Alfuzosin, Terazosin	Decreased libido, orgasmic dysfunction Ejaculatory dysfunction
3.	Lipid lowering agents	Statins and fibrates	Decreased libido
4.	Antiarrhythmic agent	Digoxin	Decreased desire, arousal and orgasmic dysfunction
5.	Gonadotropins	(GnRH agonists- Goserelin, Leuprolide acetate and LHRH agonists- Histrelin)	Vaginal atrophy, dyspareunia, decreased libido, hot flashes
6.	Antiandrogens	Cyproterone acetate, Finasteride, Dutasteride, Ketoconazole	Decreased desire, arousal, orgasmic dysfunction and non-specific sexual difficulties
7.	Contraceptive drugs	Injectable Progestins and MDPA Oral contraceptives	Atrophic vaginitis, dyspareunia, weight gain, depression Decreased libido, hirsutism, acne and weight gain, depression
8.	Alpha interferon		Non-specific sexual dysfunction: Prevalence of 1-3%. Amenorrhea, pelvic pain, decreased libido

9.	5HT3 receptor antagonists	Alosetron	Non-specific sexual dysfunction
10.	Antacids	Ranitidine, Cimetidine, Famotidine	Decreased levels of circulating testosterone-decreased sexual desire and arousal
11.	Steroids	Prednisolone	Weight gain, depression, decreased testosterone levels, decreased desire, ED
12.	mTOR inhibitors	Sirolimus, Everolimus	ED, non-specific sexual side effects.
13.	Protease inhibitors	In HAART	ED

ED- Erectile dysfunction/ ACE- Angiotensin converting enzyme/ MDPA- Medroxyprogesterone acetate/ HAART- Highly active antiretroviral therapy

Management of drug-induced SD

1) Addressing sexual functioning, patient's expectations, fantasies, lifestyle, and partner-related factors. Patients should be encouraged to lead a healthy lifestyle, exercise, and adhere to treatment of physical illnesses. This may enhance their overall physical and mental health, overall wellbeing, and self-image.
2) Providing proper information can dispel fears, misconceptions about sexual problems.
3) Considering medication with a lower probability of associated SD especially in sexually active individuals. During treatment, active monitoring of sexual functioning is important.
4) Reducing the dose of medication to the lowest effective dose.
5) Advising to schedule sexual activity around the dose of medication.
6) Switching to another medication from the same class with a lower propensity to cause SD. For example, if beta blockers are being used as antihypertensives, switching to a cardio selective agent such as Nebivolol may help reduce SD.
7) Employing drug holidays.
8) Administering specific antidotes, if available.
9) Administering Phosphodiesterase inhibitors such as Sildenafil when indicated.
10) Adjunctive or alternative treatment with Cognitive Behavioral therapy, supportive therapy, or sex therapy.
11) Advising exercise in daily lifestyle and before sexual activity.
12) Use of mechanical interventions such as vacuum pumps, vibrators, etc.
13) The guidelines for the management of SD associated with cardiovascular medication and antihypertensives are not very clear. However, the main recommendations seem to be to either switch to another drug with a better safety profile such as calcium channel blockers or angiotensin-converting enzyme inhibitors/Captopril or to add a phosphodiesterase

inhibitor. The addition of PDE5 inhibitors to usual common antihypertensive medicines (diuretics, beta blockers, calcium blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) results in either no or small additive reductions in blood pressure (BP) and no increase in serious clinical adverse events. However, the combination of organic nitrates and PDE5 inhibitors should be avoided entirely because of synergistic and symptomatic reductions in BP.

To conclude, a risk-benefit analysis should be done for any pharmacological agent associated with SD and wherever possible, the offending agent should be stopped or switched to an agent with a better tolerability profile.

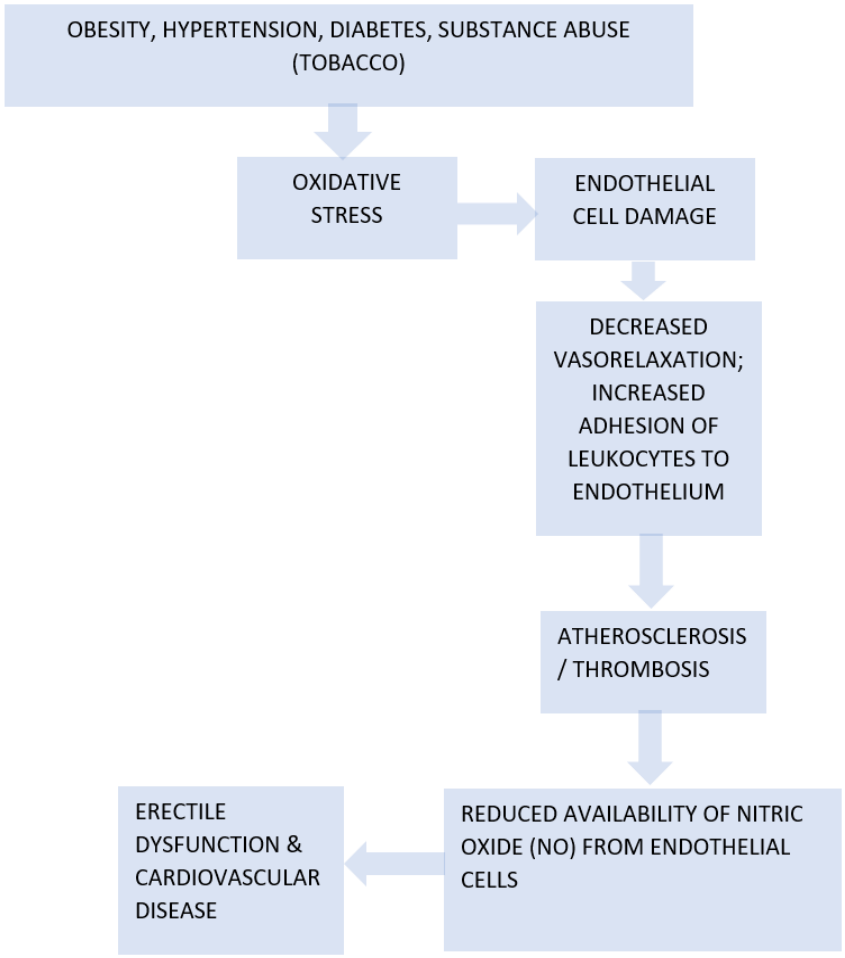
6. SEXUAL DISORDERS AND CARDIOVASCULAR CONDITIONS

Vascular causes of Erectile Dysfunction

The most common link between cardiovascular disorders (CVD) and erectile dysfunction (ED) is endothelial injury. The artery size hypothesis explains that endothelial injury and stenosis of all vascular beds due to atherosclerosis limits the flow of blood. Smaller vessels (penile arteries; 1-2 mm diameter) are unable to adapt to the same extent when compared to larger vessels (coronary arteries; 3-4 mm diameter). A vascular compromise in the penile arteries due to atherosclerosis leads to ED.

The etiopathogenesis of ED of CVD and ED has been explained in **Figure 3**

Figure 3: Common etiopathogenesis of cardiovascular disorders (CVD) and erectile dysfunction (ED)



Coronary artery disease (CAD) affects sexual functioning of both men and women conspicuously over a period of six months has been briefed in **Table 8.** (Schwarz ER, Kapur V 2008)

Table 8: Coronary artery disease (CAD) and sexual functioning of males and females over a period of six months

MALES	FEMALES
Difficulty maintaining an erection after penetration(~84%)	Arousal disorder (~87%)

Reduced sexual desire and excitement (~76%),	Decreased vaginal lubrication (~84%)
Difficulty reaching orgasm(~62%)	Difficulty reaching orgasm (~62%)
Difficulty having an erection for penetration (~84%)	Sexual pain (~50%)
	Reduced sexual activity(~29%)

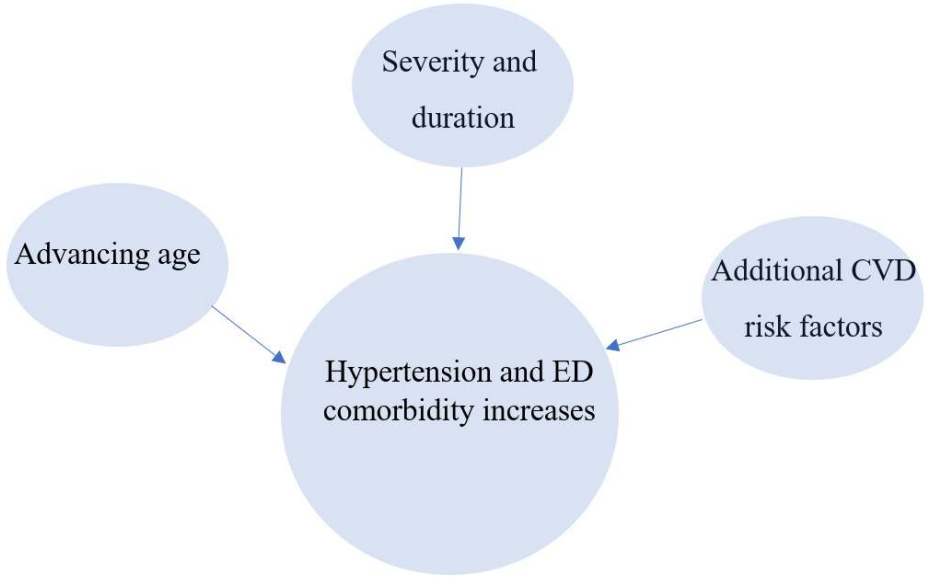
Hypertension

Arterial hypertension is strongly associated with ED and is a major risk factor for CVD. The prevalence of ED in hypertensive individuals is approximately double than that in normotensive population.

The comorbidity of ED and hypertension increases with age, severity and duration of hypertension and presence of other CVD risk factors as shown in **Figure 4**. (Doumas M, Tsakiris A 2006)

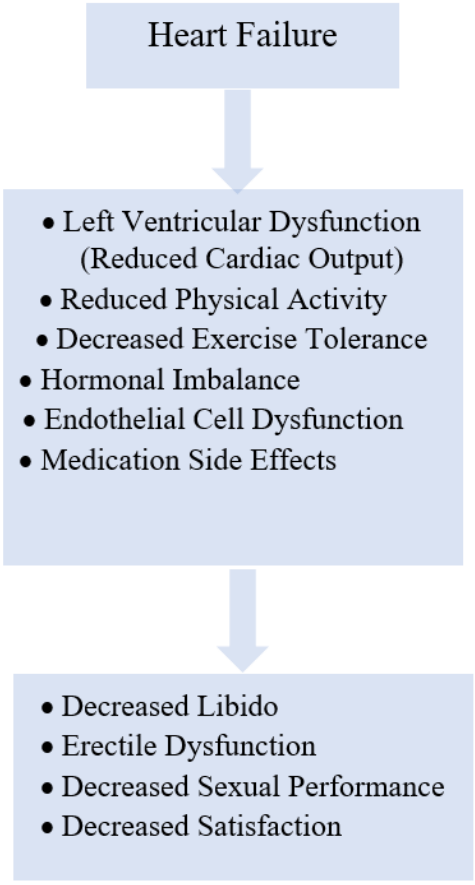
ED prevalence is double in men with systolic blood pressure (SBP) > 140 mmHg when compared men with SBP < 140 mmHg. Pelvic arterial insufficiency is the major cause of ED in elderly aged over 50 years. Narrowing of any part of erection related arterial axis (iliac-pudendal-penile arterial system) could lead to ED. ED is a marker of asymptomatic coronary artery disease (CAD) and may precede the development of CAD by 3 to 5 years.

Figure 4: Comorbidity of HTN (Hypertension) & Erectile dysfunction: Risk factors



Heart failure

Figure 5: Pathophysiology of sexual dysfunction in Heart Failure



Myocardial Infarction

Post MI a significant number of individuals develop sexual dysfunction. A number of researchers have studied sexual functioning post MI. However, during this period they remain under informed about their sexual concerns. Even at one year follow up only 41% of patients and 31% of their partners had received information about their relationships, sexual health and how to resume sexual activity, during the cardiac rehabilitation process. Sexual education plays a vital role for individuals, in resuming their sexual activity. Sexual performance related anxiety and difficulty getting aroused due to vaginal dryness may me present post MI.

7. SEXUAL DISORDERS AND CANCER

The prevalence of cancer has been increasing with approximately 10 million deaths occurring worldwide in 2020.The most common cancers in men include lung, prostate, colorectal, stomach and liver cancer whereas women are more prone to breast, colorectal, lung, cervical and thyroid cancers. There is an increase in cancer burden which affects not only the individual and the family but also the health care system. Improvement in facilities and early detection have helped in cancer survival, though many survivors still face the challenges of navigating lives in various domains. The impact on interpersonal relationships, intimacy and sexual concerns would not be of primary importance to the cancer survivor and hence that domain of life would remain impaired. This would be most affected in patients with breast, cervical and prostate cancers but as is commonly seen in other patients of sexual dysfunctions, most patients and relatives would be hesitant to broach the problems associated with sexual functioning.

Most oncologists may not be aware of asking about sexual functioning though sexual satisfaction is important for a better quality of life. Hence psychiatrists or counselors should therefore address these issues when seeing patients of cancer or cancer survivors.

How does Cancer affect Sexuality?

Cancer as an illness has severe burden and clinical outcomes which affects the patients physically, biologically and emotionally. A patient afflicted with cancer and undergoing cancer treatment would show different responses to sexuality depending on the phase of detection or treatment of cancer. Hence the sexual dysfunctions could be related to any phase and hence it becomes vital to assess the same. Cancer treatment is also very rigorous involving surgery, chemotherapy and radiotherapy which result in anatomical changes, body image issues, emotional changes all of which affect the patient's perception to self, partner, relationship and quality of life. Many oncologists are focused on the treatments for life threatening cancer and may underestimate the psychological effects on the cancer survivors. With improved cancer care and aging population there are many cancer survivors. Hence it becomes important to improve their sexual health which is an integral part of quality of life.

Sexual dysfunctions occurring due to the various treatment options:

a. *Surgery related sexual dysfunctions in males and females (Table 9)***:**

Treatment options	Male	Female
Surgery: Genitourinary Cancers		
Cervical cancers: Radical hysterectomy		Dyspareunia Innervation problems
Vulval/Vaginal cancers: Large excisions		Difficulty in penile-vaginal intercourse

		Nerve injuries due to excisions can cause reduced sexual arousal and orgasm
Oopherectomy		Iatrogenic menopause in premenopausal women leading to arousal disorders Low desire
Surgery: Breast Cancer(Mastectomy/breast conserving surgery)		Reduced breast stimulation leading to desire, arousal difficulties Body image problems, appearance related concerns, being feminine
Surgery: Head /Neck cancers/Breast cancers	Anatomical changes, disfigurement, lack of attractiveness, body image problems, embarrassment, desire and arousal problems	
Prostate Cancer: Prostatectomy(nerve sparing) TURP	Erectile dysfunction Anejaculation,delayed, orgasm,less intense orgasm,anorgasmia Retrograde ejaculation	
Low resection of rectal tumors	Erectile dysfunction	
Bladder surgery	Erectile dysfunction, Anejaculation	
Retroperitoneal lymphadenectomy in testicular cancer	Anejaculation	
Abdominoperitoneal resection/ Sigmoidectomy in colorectal cancers	Anejaculation	
Surgical complications : enervation/ ischemia	Fibrosis & erectile dysfunction	

b. *Chemotherapy:* Chemotherapy is known to have severe side effects as it also affects normal cells. All patients of cancers do undergo a course of chemotherapy which results in hair loss, mucositis, weakness, tiredness, fatigue and gastrointestinal symptoms. These side effects have an impact on the emotional status of the individual and therefore may lead to an overall decreased interest or desire in sexual activity. Due to hair loss, changes in hair and skin texture body image concerns arise along with reduced self-esteem,and feelings of embarrassment especially in breast

cancer survivors. This therefore affects the sexuality of the individuals. Some chemotherapeutic drugs are also known to affect infertility due to their effects on the gonadal tissue. Premature menopause is also seen in women & girls exposed to treatments which results in reduced desire

c. *Radiation therapy:* Radiation therapy is known to result in scarring of the affected tissue along with vascular damage. Radiation to normal tissues also results in this damage. Very often sexual dysfunction results due to radiation therapy given to gonadal or genitourinary cancers. Radiation therapy to prostate cancers may result in erectile dysfunction mostly 1 year later and are often seen 3-5 years of treatment. This is because radiation causes damage to the blood vessel lining and nerves and sometimes the erectile tissue, due to which they cannot hold the blood during erection, resulting in venous leaks. Pelvic radiation also results in premature ovarian failure causing low desire in women cancer survivors.

d. *Hormone therapy:*
Hormonal treatments which are given to reduce the growth of hormone sensitive tumors result in disruption of the hormonal axis. Hence hormonal treatments of breast and prostate cancers may result in reduced sexual desire, arousal and impairment in sexual functioning.

Impact on Sexual functioning
Cancer and its treatment have been known to affect all areas of sexual functioning.

- Table 9 mentions the various sexual dysfunctions seen in different cancers.
- Self-image is an important aspect which is affected in patients with cancer. Appearance related concerns due to scarring & disfigurement in breast cancers are commonly seen in breast cancer survivors. Several researchers have noted that women feel “less sexually attractive’ and less feminine after cancer treatments. Also several breast and gynecologic cancer survivors had a negative “sexual self-schema” which would be the cognitive representation of one’s sexual beliefs ,attributes and sexuality. This often resulted in poorer sexual outcomes as the negative schema is known to impact sexual functioning and behavior.
- Low sex drive has been seen in breast cancer survivors and some studies have reported a fear/aversion to sexual activity post treatment.
- Mood disturbances like depressed mood, fatigue, reduced interest are seen in patients of cancer and those undergoing treatment which may further cause a loss of libido. Treatment with antidepressants is also known to worsen the sexual functioning.
- Fear about resuming sexual activity is often seen in patients and their partners due to concerns regarding sex causing tissue damage or interfering with the healing process.
- Lack of awareness /knowledge /incomplete information about the procedure, its impact on organ functioning or anatomical correlates may often result in misconceptions in patients and their partners.

- Poor communication between partners prior to the illness may further worsen the communication process post treatment and the partners' fears or concerns could be mistaken for lack of interest or attraction.
- Survivors of HPV (human papillomavirus) cancers often experience shame, guilt and stigma as they know it is sexually transmitted. They have anxiety about sexual activity and hence also refrain from sexual activity as they fear recurrence.

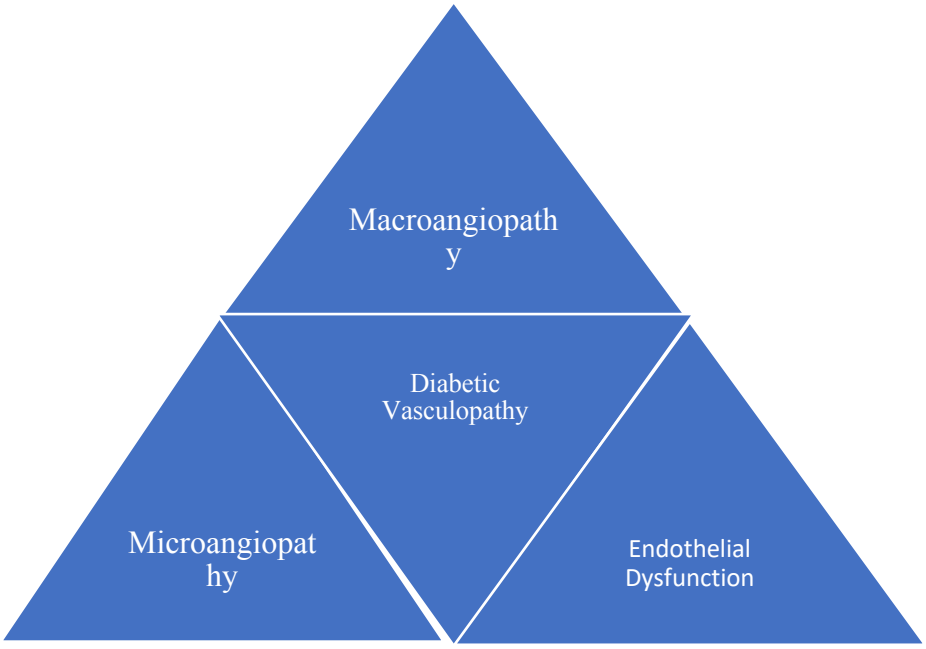
Sexual dysfunction in cancer and post cancer survivors is an important aspect that needs to be looked into by the oncologist in liaison with the psychiatrist. Importance needs to be given to sexual health which helps to improve the overall quality of life. Creating awareness among the oncology colleagues, timely assessment of cancer patients and treatment of the sexual dysfunctions would help in improving health related outcomes in the post cancer survivors.

8. SEXUAL DISORDERS AND ENDOCRINE DISORDERS

Diabetes Mellitus

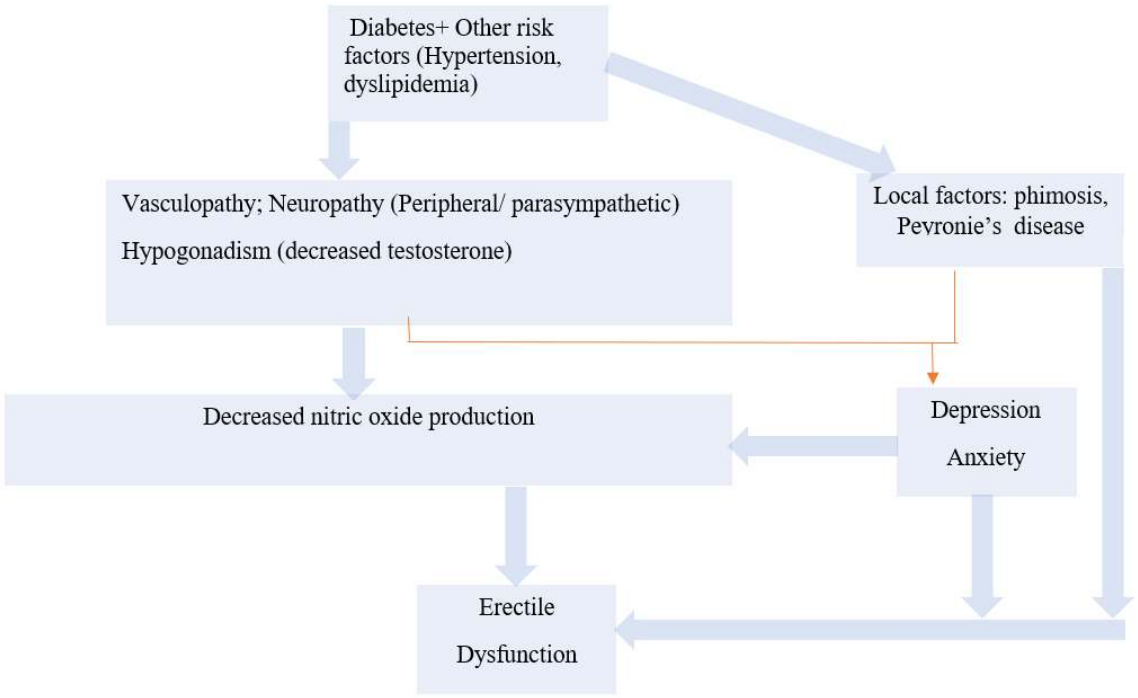
ED due to diabetes can be classified as an endocrine system related problem as well as under vascular causes of ED. Diabetics (type 1 and 2) are at a three times higher risk for ED when compared to non-diabetic individuals as concluded by MMAS (Massachusetts Male Aging Study). Diabetes induced ED is of multifactorial origin as shown in **Figure 6.**

Figure 6: Pathogenesis of erectile dysfunction in Diabetes



Diabetic vasculopathy encompasses microangiopathy, macroangiopathy and endothelial dysfunction. Macrovascular disease due to atherosclerosis damages the blood vessels limiting flow in the vascular beds.
Male sexual dysfunction (SD) due to diabetes includes ED, desire/ arousal problems and orgasmic/ ejaculatory dysfunction. ED prevalence in diabetic men varies from 35% to 75%. ED as a consequence of diabetes is multifactorial in origin with metabolic, vascular, neurological, hormonal, and psychological components as explained in **Figure 7.** (Tamás V, Kempler P 2014, Malaviqe LS, Levy JC 2009)

Figure 7: Pathophysiology of Erectile Dysfunction in Diabetes Mellitus



In diabetics the sensory information from the penis to the spinal and supraspinal centres is impaired. Associated impaired parasympathetic inactivity further worsens erection. In diabetics, strict glycaemic control is advised to avoid ED. Reversal of ED even if diabetes is strictly controlled is not very successful. In females, the association of diabetes with SD is not very conclusive. However, the prevalence of SD is much higher in females with diabetes when compared to non-diabetics. Female SD is more related to psychosocial factors associated with diabetes.

Neuroendocrine system and sexual dysfunction

The human neuroendocrine system includes the HPA (Hypothalamic Pituitary Adrenal) axis, HPG (Hypothalamic Pituitary Gonadal) axis, HPT (Hypothalamic Pituitary Thyroid) axis and Hypothalamic-Neurohypophyseal system. Alteration in any of these four axis can lead to sexual problems. The HPA axis is strongly linked to the reproductive system. The hypothalamic-pituitary-adrenal (HPA) axis and the female reproductive system are intertwined and are responsible for the "hypothalamic" amenorrhea of stress, eating disorders, and the hypogonadism of Cushing's syndrome. The hypothalamic-pituitary-gonadal (HPG) axis plays a central role in the neuroendocrine system, linking the brain with the gonads. The HPG axis controls the various aspects of sexual function; excess or deficiency of pituitary hormones or metabolic alteration associated with pituitary diseases (Cushing's disease) can lead to ED.

Endocrinopathies associated with ED include thyroid dysfunction, hypogonadism and hyperprolactinemia. Androgen deficiency has been noted in 2 to 33 % of men with ED. The most common endocrinopathy in ED patients is low testosterone levels (15%) followed by hyperprolactinemia (13.7%) and hypothyroidism (3.1%). The diagnosis of endocrinopathies is based on blood hormone levels.

Both hypothyroidism and hyperthyroidism are associated with sexual dysfunction (SD) in both the sexes. The prevalence and type of sexual dysfunction is mentioned in **Table 10.** Thyroid hormone may have a direct effect on ejaculatory process or a secondary effect of testosterone. Both hypothyroid and hyperthyroid state can alter circulating sex hormone levels through peripheral and central pathways which lead to sexual problems. In hypothyroidism, the disruption of hypothalamic-pituitary adrenal axis leads to decrease in sex hormones, both free and total testosterone levels leading to sexual problems.

Table 10: The prevalence and type of sexual dysfunction associated with thyroid disorders

Thyroid disorder	**Males**	**Females**
Hypothyroidism		
Prevalence	59 to 63%	22 to 46%
Type of SD[#]	Erectile and ejaculatory dysfunction (delayed ejaculation) Impaired libido	Impaired libido Impaired desire, arousal/lubrication, orgasm, satisfaction, and pain during intercourse
Hyperthyroidism		
Prevalence	48-77%	44 to 60%

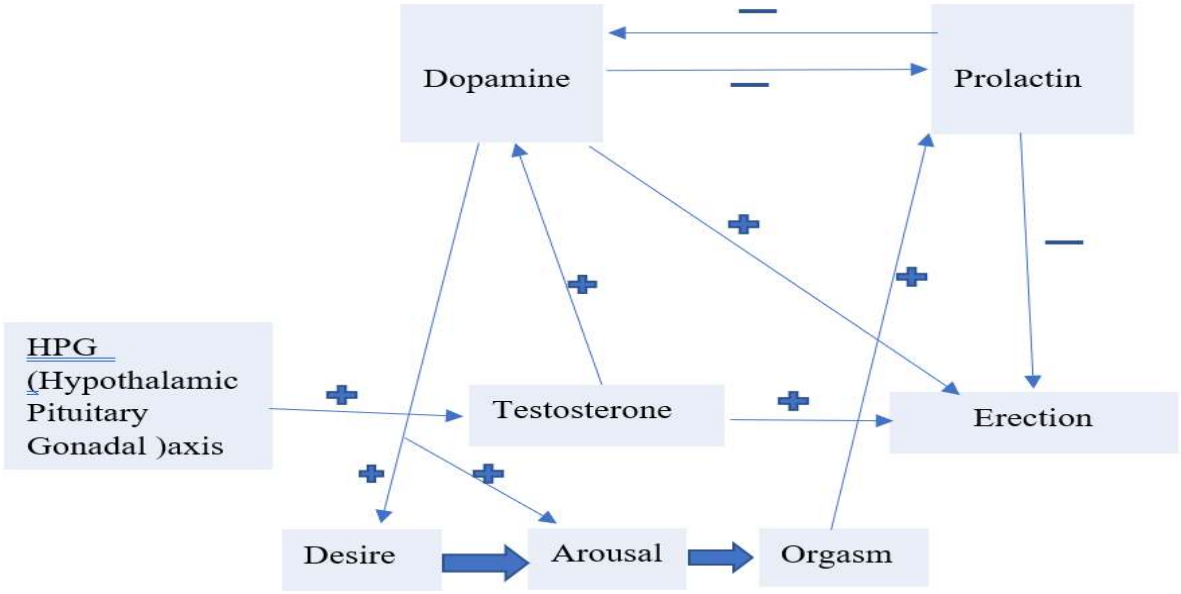
Type of SD[#]	Erectile and ejaculatory dysfunction (premature ejaculation) Impaired libido	Impaired libido Impaired desire, arousal/lubrication, orgasm, satisfaction, and pain during intercourse

#SD-Sexual Dysfunction

Hypogonadism can occur due to any insult to the HPG axis. Thus, hypogonadism can be primary (Klinefelter's syndrome and cryptorchidism) or secondary (i.e., central dysfunction which includes head trauma, prolactinoma, pituitary surgery, drug abuse). Hypogonadism can be effectively treated with testosterone replacement therapy (TRT) which improves sex drive and enhances phosphodiesterase (PDE-5) inhibitor effectiveness.

The hormonal conditions required for ejaculation are complex. Androgen receptors are present throughout the body including the areas of the brain associated with arousal and orgasm. Low testosterone levels are associated with delayed ejaculation (DE) and higher levels of the same are linked to premature ejaculation. Prolactin can be considered as a surrogate marker of serotonin activity. High levels of prolactin supress ejaculation. During ejaculation dopamine peaks (during orgasm and climax) and prolactin is suppressed. Once orgasm is over prolactin spikes and dopamine decreases. Prolactin is partially responsible for the refractory period in men. Hence both prolactin and dopamine levels are inversely related. Hyperprolactinemia occurs in 1 to 5 % of men with ED. Around 50% men with microprolactinomas and 75% of men with macroprolactinomas report either reduced sexual desire or ED. Hyperprolactinemia in women can be associated with reduced sexual arousal, lubrication, orgasm, and satisfaction. The relationship between dopamine, prolactin and testosterone is shown in **Figure 8.**

Figure 8: The relationship between dopamine, prolactin and testosterone



Prolactin is involved in control of sexual behaviour by modulating the effects of dopaminergic and serotoninergic systems on sexual function. A short term or long-term increase in prolactin can control CNS sexual function by acting directly on receptors in the brain and possibly affect erection in men and response of genitalia in women. A chronic increase in prolactin levels is associated with hypogonadotropic hypogonadism and SD in both sexes. Growth hormone (GH) is an important regulator of HPG axis and possibly regulates sexual response of genitalia in both men and women. Both in GH deficiency and excess a decrease in desire and arousability is present (in both the sexes) with impaired erection in men.

Hypersexuality and hormonal imbalance

Hypersexual disorder (HSD) (not included in DSM-5; Diagnostic and Statistical manual of mental disorders, 5th Edition) is a diagnostic label given to a range of behaviours which are a result of intense sexual urges or fantasies and cause significant distress or socio-occupational dysfunctioning. Clinical presentation may include excessive sexual activity or intercourse, masturbation, pornography or computer assisted sexual activity. HSD can be considered as a type of compulsion, addiction, or impulse control disorder. Other names for HSD include hypersexuality, erotomania, compulsive masturbation and sexual compulsivity. Common medical conditions which may be associated with hypersexual behaviour are listed in **Table 11.** HSD neurobiology involves the thalamus, mamillary body, amygdala, prefrontal region, cingulate gyrus, hippocampus, nucleus accumbens, caudate nucleus and brainstem (VTA: ventral tegmental area, raphe nuclei, substantia nigra.

Table 11: Comorbid medical conditions associated with hypersexuality

Neurological disorders	Kluver-Bucy syndrome, partial complex seizures, frontal lobe lesions, traumatic brain injury

Neuropsychiatric conditions	Sexual disinhibition in dementia and delirium
Psychiatric disorders	Bipolar mood disorder, schizoaffective disorder, attention deficit hyperactivity disorder, borderline personality disorder
Substance abuse	Methamphetamine, alcohol
Drugs	Dopaminergic agonists
Psychological	Stress: Altered Hypothalamic Pituitary Axis Childhood and adolescence psychological abuse

It is important to note the following points of HSD. (1) whether it is a distinct disorder (as yet unrecognized) (or problematic psychosexual behavior) (2) a symptom of an existing disorder or medical condition (4) normophilic activity at the high end of sexual functioning. The sexual behavior cycle of HSD includes sexual incongruence and cognitive abeyance. A sexual urge leads to sexual behaviour and sexual and post sexual satiation. This is again followed by sexual urge when the cycle repeats.

Though hypersexual disorder could not make it to DSM-5, criteria proposed for the same by Reid and Colleagues have been briefed in **Table 12.** (Reid RC, Carpenter BN, Hook JN 2012) Kaplan and Krueger have explained subtypes of HSD as mentioned in **Table 13.** (Kaplan MS, Krueger RB 2010)
Treatment algorithm to HSD is mentioned **in Figure 9.** (Reid RC, Garos S 2011; Khan O, Ferriter M, Huband N 2015, Tierens E, Vansintejan J 2014)

Figure 9: Treatment Algorithm for hypersexual disorders

SSRIs: Selective Serotonin Reuptake Inhibitors; TCAs: Tricyclic antidepressants
LHRH (Luteinizing hormone- releasing hormone); GnRH (Gonadotropin-releasing hormone); im: intramuscular

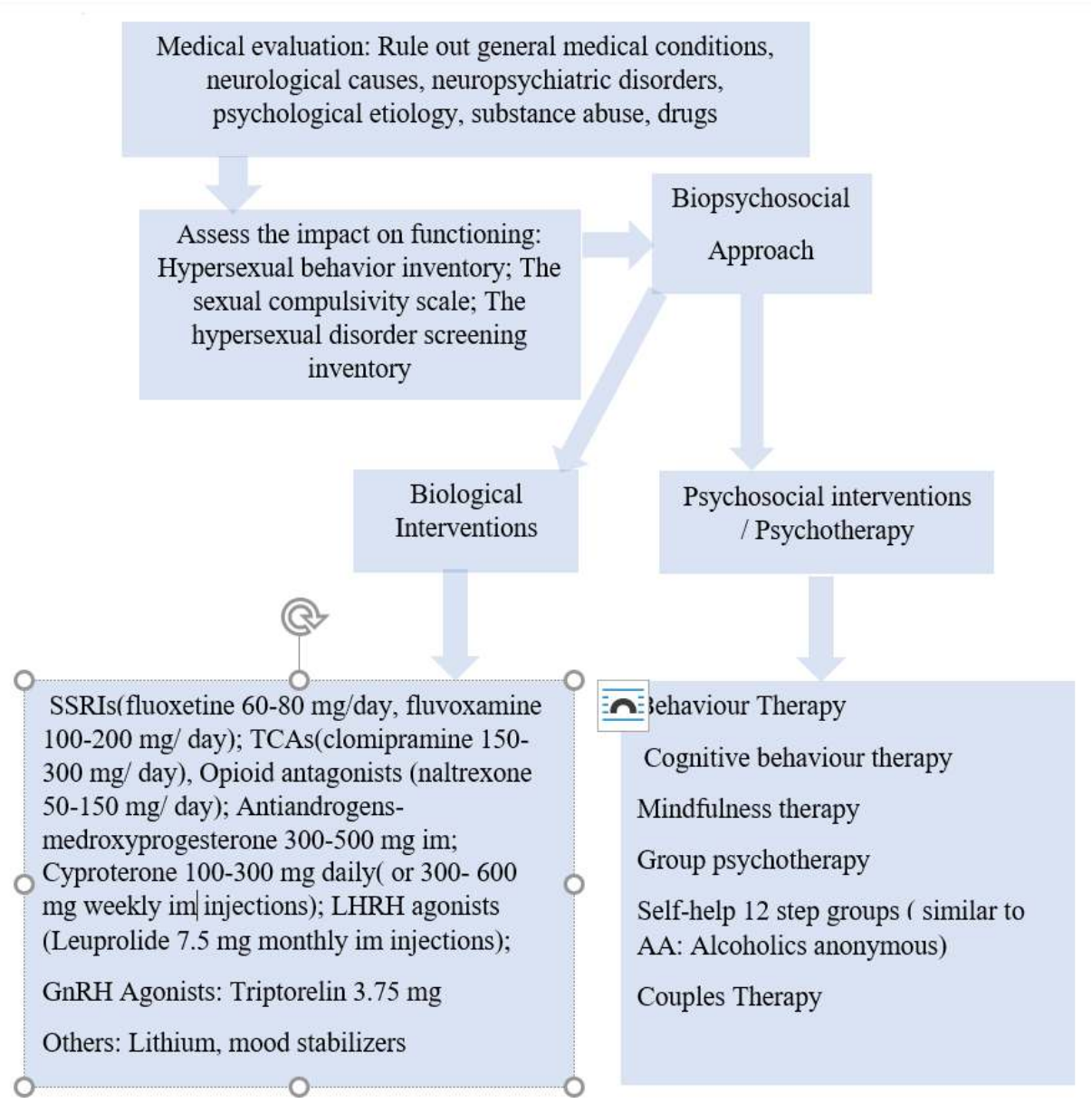


Table 12: Proposed criteria for DSM-5 hypersexual disorder
A. Over a period of at least 6 months, 'Recurrent and intense sexual fantasies, over a period of 6 months with >= 4 of the following five criteria:'
1. 'Excessive time is spent on sexual fantasies, planning and performing the act.'
2, 3. 'Repeatedly engaging in sexual fantasies or behavior in response to either dysphoric mood state or stressful life events'
4. 'Repeated efforts to control urges or behavior are not successful'
5. 'Repetitively engaging in sexual behavior, irrespective of the physical or emotional risk involved.'

B. ‘There is associated significant distress or socio-occupational impairment’
C. ‘These behaviors are not substance induced and not due to a general medical condition’
D. ‘The person should be 18 years of age’
Specify : Type of Hypersexual disorder

Table 13: Subtypes of hypersexual disorder

1. Excessive masturbation: in ranges from 50 to 75%.
2. Pornography: 50–60% of patients with HSD are dependent on pornography (Reid RC, Carpenter BN 2009)
3. Sexual behavior with (consenting) adults: Reid et al., in 2009, concluded that 7% (of males seeking treatment) solicited sex workers regularly, 12% had unprotected (multiple innominate) sex, and 21% had extramarital affairs. (Reid RC, Carpenter BN 2009)
4. Cybersex: Includes online ‘sexual conversations’ in chat rooms or ‘text-messaging applications : sexting’.
5. Telephone sex: Studies done two and a half decades back concluded that around 37% of males struggling with HSD had excessive telephone sex .
6. Strip clubs: Many individuals with HSD are dependent on strip clubs with excessive alcohol use and guilt.

9. Sexual disorders and other chronic physical illnesses (Table 14)

Table 14: Sexual disorders and other chronic illnesses

S.no.	Category	Mechanisms	Manifestations
1.	Chronic pain - Psychological factors	Decreased sense of self-esteem, sexual desire and feelings of desirability. Comorbid depression and anxiety.	Decreased libido.
	- Physiological factors	Direct injury to nerves and adnexa due to surgery and physical trauma.	Decreased arousal, erectile dysfunction, dyspareunia.

		Radiation therapy, nerve blocks and other surgical procedures may cause difficulties with sexual intercourse.	
	- Pharmacological factors	Analgesic medication may have sexual side effects. Opioid preparations, sedatives, antispasmodics and antidepressants may also compound the sexual distress due to the pain.	Decreased libido.
2.	Chronic inflammatory conditions	Inflammatory bowel disease, Rheumatoid arthritis, Fibromyalgia among other chronic inflammatory conditions have been associated with an increase in the levels of C-reactive Protein which may interfere with arousal via direct (neuronal) and indirect (endocrine, vascular) mechanisms. There may also be associated pain, restriction of movement and fatigue.	Decreased libido, reduced mobility, erectile dysfunction and difficulties with arousal.
3.	Sexually transmitted diseases	Chlamydia associated chronic prostatitis.	Premature ejaculation and erectile dysfunction in men.
		Chlamydia and Gonorrhea associated Pelvic inflammatory disease.	Dyspareunia, infertility in women.
		HIV therapy	

		Genital Herpes	Decreased libido Comorbid psychiatric illnesses, non-specific sexual dysfunction.
4.	Chronic Respiratory illnesses	Chronic Obstructive Pulmonary disease, Interstitial Lung disease, Lung cancer- Decreased exercise tolerance, fear of dyspnea, decreased testosterone levels and increased cardiopulmonary load.	Decreased sexual desire, erectile dysfunction in men. Decreased sexual desire, anorgasmia and painful intercourse in women.

10.SPECIAL CONSIDERATIONS

Gender dysphoria and Gender affirming/confirming surgery

Gender dysphoria has replaced gender identity disorder in DSM V and it is signifying a marked sense of unease that a person experiences with the biological sex and ones' gender identity. The distress may be so severe that it can impair social & occupational functioning and may also cause anxiety /depression in the person. Gender nonconformity is not a mental disorder by itself, but if there is distress arising from it, then it needs to be evaluated. Many patients of gender dysphoria want to change their biological sex to conform to their sexual orientation. Gender dysphoria has also been seen in adolescents and children and also includes disorders of sex development (DSD) where children are assigned genders by parents or physicians.

Though the number of people coming out in the open about their gender dysphoria has risen, there is still social stigma associated with gender nonconformity and cultural differences due to which the gender dysphoric individual faces a lot of mental health issues. Also due to the lack of teaching about the same in medical schools along with reduced importance, several medical professional bodies have to depend on the World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) and the Endocrine Society (ES) guidelines for the treatment of gender dysphoria. The goals of treatment include to resolve the distress experienced by the patient and to affirm his/her gender identity. This approach therefore requires a multidisciplinary team which includes a mental health professional (MHP)- psychiatrist & psychologist/counselor, plastic surgeon, endocrinologist, urologist and gynecologist in adult patients and also a pediatrician and pediatric endocrinologist for children and adolescents with gender dysphoria. Treatment parameters have been included in **Figure 10.**

Figure 10: Treatment parameters for Gender dysphoria and Gender affirming/confirming surgery

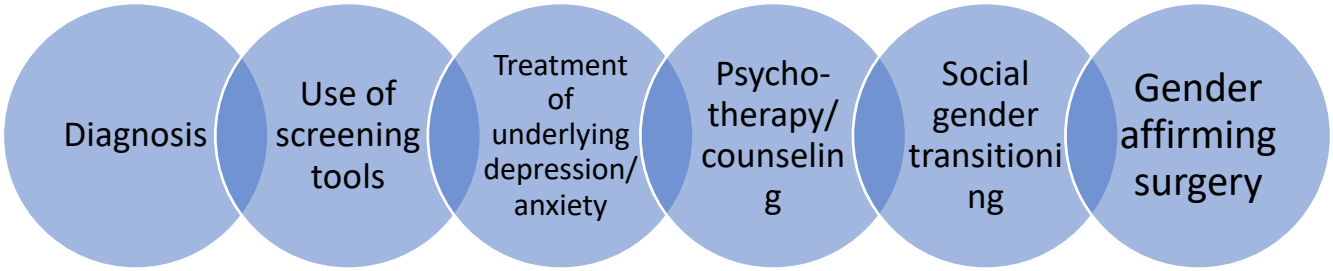


Table 15 describes the role of a MHP as per WPATH SOC version 7 and ES guidelines.

Table 15: Role of MHP as per WPATH SOC version 7 & ES guidelines:

Only a qualified MHP should diagnose gender dysphoria.
A detailed psychological evaluation with screening tools or psychological tests to be done for gender dysphoria.
MHP should be trained in assessment and treatment of transgender or gender nonconforming patients.
If MHP not available, then other medical professionals can also diagnose if they had training in gender and mental health issues.
Diagnosis is as per DSM V or ICD 11 criteria; psychosocial functioning should also be examined.
MHP discusses treatment options for gender dysphoria and concomitant mental disorders.
To psychoeducate patients about gender identity, gender expression and evaluate their comfort in gender expression and assess social support systems.
As per WPATH SOC v7 MHP can ask the patient to do social transition or have real life experience of living full-time as his/her preferred gender identity in all aspects of his/her life at least for a year. Social transition is important as the patient knows what to expect in his/her personal life, from families, workplace and community. This phase is reversible and hence important before he/she takes the step for surgery.

MHP should document these aspects of social transition in a regular follow up detailing the timeline, coping and patient's commitment. This information can be used to provide counseling to the patient or strengthening his support systems. Family education and counseling also helps. Patient can then be referred for hormonal therapy.
Provide appropriate referrals for hormone therapy if patient meets WPATH SOC readiness and eligibility criteria; liaison with the endocrinologist/ specialist to assess patient's expectations from hormonal therapy.
Cross -sex hormone therapy is initiated as a treatment modality for gender dysphoria to induce secondary sexual characteristics as per patient's desired gender and minimizing those of their biological gender for at least 12 months. This also helps in improving the quality of life, sexual functioning, reducing psychopathology, easing social transition and giving some relief from gender dysphoria. MHP also need to continue ongoing psychotherapy for 12 months.
A record of the hormone therapy needs to be maintained and is a requisite for some gender affirming surgeries.
If patient wants to consider gender affirming / confirming surgical procedures, then patient should be referred to appropriate surgeons if patient meets WPATH SOC readiness and eligibility criteria.
WPATH SOC requires 2 referral letters from MHP for surgery which document persistent gender dysphoria, capacity to make a fully informed decision and give consent for treatment with patient achieving legal age of maturity in a given country. Any associated medical or psychiatric co-morbidity should also be adequately controlled.
WPATH SOC encourages individualized treatment and hence surgeons and patients should discuss options as per patients goals for gender expression, realistic expectations from surgery, cost, aesthetics, postoperative care, recovery, complications etc.
WPATH SOC does not require referral letters if the patient wants facial feminization or masculinization procedures or thyroid laryngoplasty.
WPATH SOC requires 1 letter of referral from MHP for breast/ chest gender affirming surgeries.
It is important to educate patients and families about regulations for change of gender on legal documents as per the country's policies and laws.
Information and referral for peer support should also be provided.

The current laws in India as per The Transgender Persons (Protection of rights) Act, 2019 allow the procedure for gender affirming/confirming surgeries and change in name after following the proper procedure laid down in the Act. However, it still remains a continued need to establish teams that would work together to help patients of gender dysphoria. The medical curriculum also needs to be aligned to the changes and reforms taking place in different cultures and societies so as to offer teaching and learning opportunities to the medical fraternity. Creating awareness among mental health professionals and medical practitioners about the needs of the

transgender community would definitely improve the quality of care given to this minority section.

11. THE WAY FORWARD IN MANAGEMENT: MULTI-DISCIPLINARY INTEGRATION OF CARE

It is clear from the above discussion that psychosexual problems are common in medical settings where a psychiatrist need to be consulted. Though sexual dysfunction inevitably mostly comes under the purview of mental health professionals, the distinction between medical and psychological causes is often not watertight. The prognosis can have a variable course across patient populations, given significant variability within and between distinct cohorts. With that said, it is recommended that clinicians have an honest and open conversation with patients where the benefits and risk associated with treatment are discussed, as well as the potential complications related to medications or surgical procedures. Throughout this CPG it has been highlighted how sexual disorders that stem from medical conditions often result in substantial psychological toll on an individual, affecting one's sense of general well-being and quality of life. Hence, the role of a psychiatrist in such referrals is not limited to a one-time prescription but also an integration of medical and psychosocial management in sync with all the other specialties involved in the care. For example, in an individual with on cancer chemotherapy or renal failure undergoing haemodialysis, management of sexual dysfunction will be incomplete and ineffective without a continued and collaborative dialogue between the psychiatrist, patient, families and other service care providers (oncologist, urologist, nephrologist, dietician, physiotherapist, etc.). Of course, this CPG is not exhaustive. It only covers the most common medical conditions that are capable of having sexual offshoots. Virtually, directly or indirectly every other chronic physical illness can lead to psychosexual issues, the details of which are exhaustive and have been suggested in references for further reading. Nevertheless, this CPG provides an anchor for best evidence-based practice, underlying theoretical underpinnings and approach to the diagnosis and management of sexual disorders due to medical conditions. To reiterate, sexual functioning is one of the salient attributes of health and wellbeing. Thus, in any given clinical context, the appropriate diagnosis and treatment of the underlying cause for sexual dysfunction will increase the chance that a multi-disciplinary care with effective psychosocial inputs is able to restore normal sexual functioning and subsequently improve quality of life and a better living for patients and families.

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Assessment and Management of Agitation in Consultation-Liaison Psychiatry Settings

Tables

Table 1: Component Behaviours of Agitation	
Nonaggressive Behaviors	**Aggressive behaviors**
Restlessness (akathisia, fidgeting) Wandering Loud, excited speech Pacing or frequently changing body positions Inappropriate behavior (disrobing, intrusive, repetitive questioning)	**Physical** Combativeness, punching walls Throwing or grabbing objects, destroying items Clenching hands into fists, posturing Self-injury (repeatedly banging one's head) **Verbal** Cursing Screaming

Table 2: Signs for Preliminary Identification of Agitation
1. Inability to stay calm or still
2. Motor and verbal hyperactivity and hyperresponsiveness
3. Emotional tension
4. Difficulties in communication

Table 3. Etiology of Agitation	
A. Primary Psychiatric Conditions	**B. Medical Conditions**
Delirium Dementia Substance intoxication (alcohol, cannabis, cocaine, stimulants, hallucinogens, inhalants) Substance withdrawal (alcohol delirium) Schizophrenia Bipolar affective disorder Agitated depression Anxiety disorder Personality disorder-antisocial Autism/Intellectual disability Post-traumatic stress disorder	Head injury CNS infections- meningitis, encephalitis Encephalopathies (hepatic, renal, etc.) Brain tumors/metastases Stroke Wernicke-Korsakoff's psychosis Metabolic abnormalities (electrolytes, glucose, calcium, etc.) Hypoxia Toxins/Poisoning Hormonal (thyroid dysfunction) Seizure (postictal state) Adverse effects/Toxicity of mediations

Table 4 The Signs of Impending Violence (Rice & Moore, 1991)
• Provocative behavior • Angry demeanor, fixed gaze, avoidance of gaze, hostile facial expression • Loud, excited, aggressive speech • Tense posturing (e.g., gripping arm rails tightly, clenching fists) • Pacing or frequently changing body position • Aggressive acts (e.g., pounding walls, throwing objects, hitting oneself) • Behaviour of looking for an escape • Physical signs of stress (e.g., hyperventilation, sweating, tremor)

Table 5 Critical Information which must be part of the History of Presenting Illness
Timing of agitation Nature of agitation Concomitant substance use Medication details: changes, new medicines, stopped any medicine Non-compliance to medications Other medical conditions

Table 6 Common and potentially life-threatening aetiologies of the acutely agitated patient (Moore & Pfaff, 2015)	
Toxicological • Alcohol intoxication or withdrawal • Stimulant intoxication • Other drugs or drug reactions	**Metabolic** • Hypoglycemia • Hyperglycemia/diabetic ketoacidosis • Hypoxia • Hyper/hyponatremia
Neurologic • Stroke • Intracranial lesion (e.g., hemorrhage, tumor) • Central Nervous System (CNS) infection • Seizure Disorder • Dementia	**Other medical conditions** • Hyperthyroidism/thyroid storm • Shock Syndromes • Acquired Immune Deficiency Syndrome (AIDS) • Hypothermia or hyperthermia
Psychiatric • Psychosis • Schizophrenia • Paranoid Delusional Disorder • Personality disorder • Antisocial behavior	

Table 7 General Recommendations in Managing Agitation
1. Initial attempts should identify the most likely cause of agitation and establish a provisional diagnosis and specific medication for the diagnosed cause/condition. Medications as restraint can be discouraged initially before arriving at any provisional diagnosis.
2. Non-pharmacologic methods of interventions should be considered. For example, environmental modifications to reduce stimulation (low lighting, quiet room) and verbal de-escalation have to be considered, if possible, before medications.
3. Medications sold calm the patient rather than induce sleep.
4. Patient should be kept in the loop of proceedings, even if the patient is agitated. E.g., convey about the need for restraints, choice of medication, selection of room/ward, check for preference of route of medicine administration, duration of restraints, etc.
5. If the patient is cooperative to take oral medicines, then oral medication can be preferred based on resources available for managing any acute exacerbation.

Table 8 Communication/Behavioural Interventions (Onyike & Lyketsos, 2011)	
Nonverbal -Maintain a safe distance -Maintain a neutral posture -Do not stare; the eye contact should convey sincerity -Do not touch the patient -Stay at the same height as the patient -Avoid any sudden movements	Verbal -Speak in a calm, more transparent tone -Personalize yourself -Avoid confrontation; offer to solve the problem
Aligning Goals of Care -Acknowledge the patient's grievance -Acknowledge the patient's frustration -Shift the focus to a discussion of how to solve the problem -Emphasize common ground -Focus on the big picture -Find ways to make small concessions	Monitoring Intervention Progress -Be acutely aware of progress -Know when to disengage -Do not insist on having the last word

Table 9 Indications and contraindications for medical restraints and seclusion	
Indications	**Contraindications**
• Risk of imminent harm to self • Risk of imminent harm to others • Serious destruction to the environment • Patient's voluntary reasonable request • Decrease sensory overstimulation* *Only for seclusion	• Unstable medical condition • Severe drug reaction or overdose • Punishment • Staff convenience • If experienced by the patient as positive reinforcement for violence or disruptive behaviour

Table10 Adverse Outcomes Related to Medical Restraints	
Patient-Related Adverse Events	Staff-Related Adverse Events
• asphyxiation • choking/aspiration • dehydration • joint injuries • blunt chest trauma • skin problems (ex. Bruising) • cardiac arrest/death • rhabdomyolysis • thrombosis (ex. PE, DVT) • escaping restraint • escalating agitation • re-traumatization • emotional distress • feelings of humiliation, fear, dehumanization, isolation, being ignored	• spit upon • fracture or skin injury • eye injury • permanent disability • adverse emotional reactions (ex. sadness, guilt, self-reproach, retribution)

Table 11 Factors to be considered before the physical restraints
• What are the objectives of physical restraint? • What are the risks associated with particular physical restraint? • Management plan of specific anticipated risks associated with the particular restraint plan. • Consensus about the exact timing of using a specific physical restraint. • Patient-specific risk factors: age, gender, degree of cooperation, possible intoxication, any medications given, presence of cardiovascular, respiratory, neurological, or musculoskeletal disorders. • Any specific risk factors which may increase the risk of harm to the patient during restraint? • Vulnerability to significant psychological trauma, especially for minors and the elderly. • Any cultural connotations. • Availability of emergency medicines, oxygen, required medical equipment.

Table 12 Instructions to the staff carrying physical restraint
Before physical restraint -know the steps and plan clearly -adhere to the plan discussed to execute the use of physical restraint safely -ensure that mechanical and postural factors should not interfere in breathing or circulation: e.g., to avoid prone restraint or any other position in which the patient's head or trunk is bent towards their knees.
During the physical restraint -Physical force used should be as per the necessity and in a reasonable manner. -To avoid excessive physical force or verbal aggression. -Ensure and monitor ABC all the time: Airway, Breathing, Circulation. -Consciousness and body alignment have to be monitored by the clinician. -Do not put direct pressure on the neck, chest/thorax, back, or pelvic area. -Nurse/resident doctors/duty doctors must observe for indications of physical or mental distress and ensure that clinical concerns are timely and appropriately escalated and appropriate intervention is provided. -Specifically monitor patients who have received intramuscular or intravenous medication within an hour before (or during) the use of physical restraint -On period reviews, if necessary, physical restraint positions can be changed as per the need and safety of the patient. -Discontinue physical restraint as soon as it is no longer required. -Risk assessment of continuing or discontinuing the physical restraint needs to be continuously assessed and balanced.
Post-restraint debriefing After the physical restraint ends and the patient is cooperative, a debriefing session with the patient and the patient's caretakers must be conducted. This is done: -to ensure open discussion about the events that led to the use of physical restraint. -to discuss the patient’s experience of events and physical restraint. -to allow the patient to clarify any doubts or seek more details -to provide an opportunity to identify the risk factors and plan strategies for the prevention of the need for physical restraint

Table 13 Factors to be considered while choosing medications
Patient's details: Age, gender, comorbid medical conditions, substance use, allergies
Agitation details: Cause, presentation
Pharmacological considerations: route of administration, rapidity of action, duration of action, adverse effects and interaction with other medications, past good response to any particular psychotropic.
Monitoring facilities: Airway, breathing, and circulation monitoring facilities; crash cart for any medical emergency; availability of ICU and ventilator.
Patient's preference of route of administration.
Route of administration Oral: tablets or syrups can be preferred if the patient accepts. Intramuscular (IM): Helps in rapid elevation of drug plasma levels and faster onset of action, leading to an immediate reduction in agitation. Intravenous (IV) administration: This should be the preferred mode when rapid restraint is essential.

Table 14 Medications used in managing agitation

		Initial Dose mg	**Tmax* minutes**	**Can Repeat hours**	**Maximum Dose (per 24 hrs), mg**
Oral	**Risperidone**	2	One h	2	6
	Olanzapine	5-10	Six h	2	20
	Haloperidol	5	30-60	15 m	20
	Lorazepam	2	20-30	2	12
I'M	**Olanzapine**	10	15-45	20 m	30
	Haloperidol	5	30-60	15 m	20
	Lorazepam	2	20-30	2	12
	Ziprasidone	10-20	15	10mg q 2 h 20mg q 4 h	40
	Aripiprazole	9.75	One h	2	30
IV	**Haloperidol**	5	Immediate	4	10
	Lorazepam	2	Immediate	2	12

q 2 h - every 2 hours; q 4 h - every 4 hours.
Maximum doses can vary depending on the outcome.

Table 15. use of Benzodiazepines and Typical Antipsychotics in Agitation

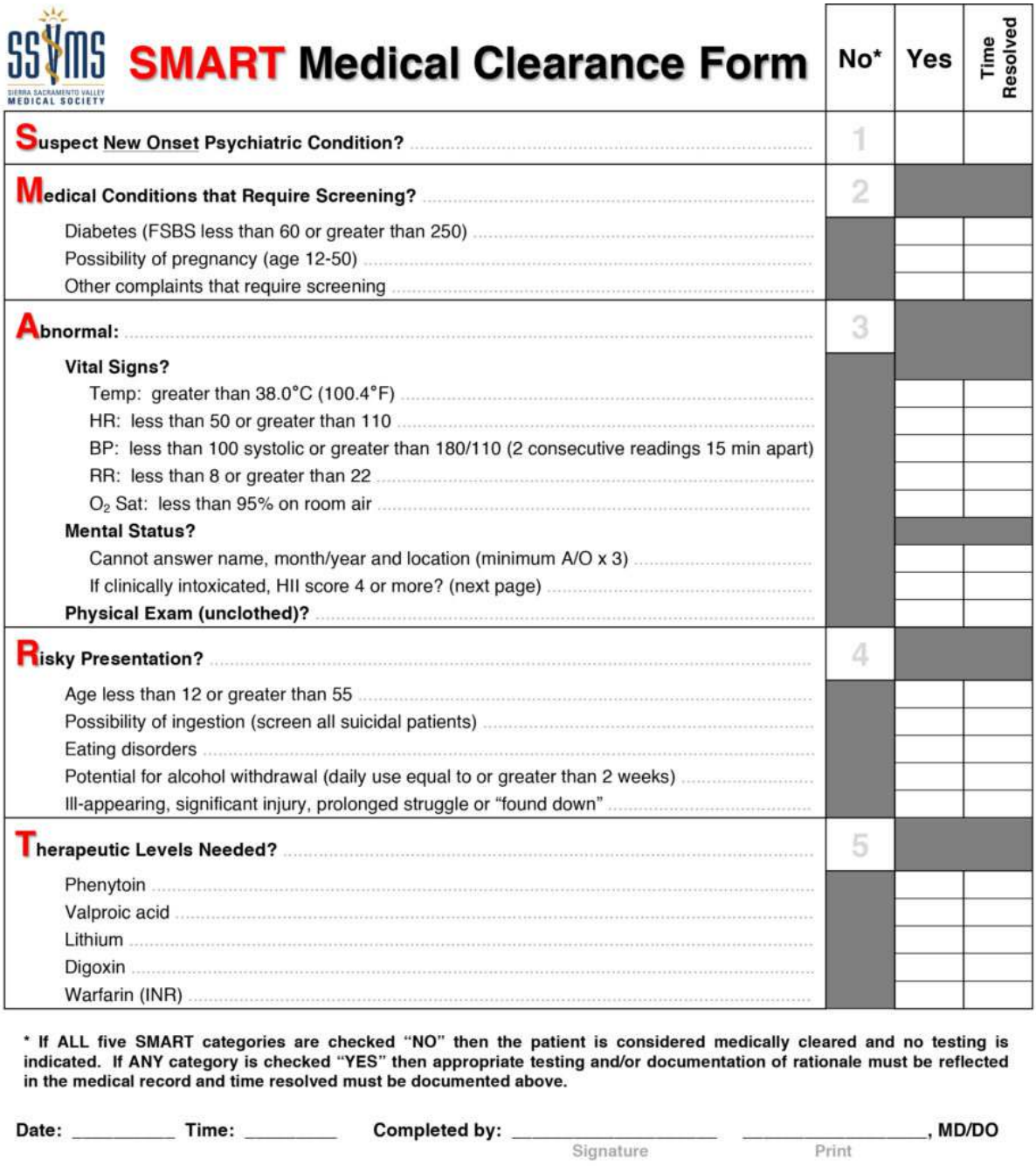
Medication Class	Medication	Dosing	Side Effects/Considerations
Benzodiazepine	Alprazolam	Only available PO Initial dose is 0.5-4 mg/day	Paradoxical reactions can be seen in character-disordered patients and can worsen symptoms in the elderly.
	Diazepam	PO, I'M, IV Start at 5 mg	Calming/sedating effect with rapid onset Use cautiously with elderly patients because of the long half-life.
	Lorazepam	PO, SL, IM, IV Start at 1 mg, moderate half-life (10-20 hr)	No active metabolites; therefore, there is a small risk of drug accumulation. Metabolized only via glucuronidation; therefore, it can be used in most patients with impaired hepatic function. Drug of choice within this class due to the moderately long half-life
Typical antipsychotics	Haloperidol	PO, IM, IV Start at 5-10 mg IM, IV	High-potency neuroleptic with favorable side-effect profile and cardiopulmonary safety. IV form is less likely to cause EPS. ECG monitoring is needed to assess torsades de pointes or QTc prolongation. The risk of NMS increases in poorly hydrated, restrained, and kept in poorly aerated rooms while given large doses of antipsychotics. Frequent vital sign checks and testing for muscular rigidity are recommended. Can cause hypotension

CVD, Cardiovascular disorder; *ECG,* electrocardiogram; *EPS,* extrapyramidal symptoms; *IM,* intramuscular; *IV,* intravenous; *NMS,* neuroleptic malignant syndrome; *PO,* per os (by mouth, orally); *PR,* per rectum; *SL,* sublingual.
Adapted from Allen M, Currier G, Carpenter D: The expert consensus guideline series: treatment of behavioral emergencies, J Psychiatr Pract 11:1-112, 2005

Table 16. use of Benzodiazepines and Typical Antipsychotics in Agitation

Medication Class	Medication	Dosing	Side Effects/Considerations
Atypical antipsychotics	Risperidone	PO, orally disintegrating tablet (OTD) Starting dose 0.5-2 mg acutely	No IM form is available Offers calming effect with the treatment of the underlying condition Orthostatic hypotension with reflex tachycardia. Increased risk of stroke in the elderly with CVD
	Olanzapine	PO, OTD, I'M; Starting dose 2.5-5 mg, max 30 mg/24 hr with doses 2-4 hours apart	Useful in patients with poor reaction to haloperidol. Calming medication with the treatment of the underlying disorder.
	Aripiprazole	PO, OTD Starting PO dose 5-10 mg, max 30 mg/day (currently IM formulation only for extended-release maintenance therapy)	Akathisia risk. Less sedating than other medications Increased risk of stroke in the elderly. Good choice for patients with QT interval prolongation
Combinations	Haloperidol, lorazepam, diphenhydramine, or benzatropine	5 mg IM, 2 mg IM, 50 mg IM, 1 mg IM	Most commonly used in the acute setting. Young athletic men are at increased risk for dystonia. Akathisia must be considered if agitation increases after administration.

Figure 1 SMART Medical Clearance Form



SSVMS Sierra Sacramento Valley Medical Society

SMART Medical Clearance Form

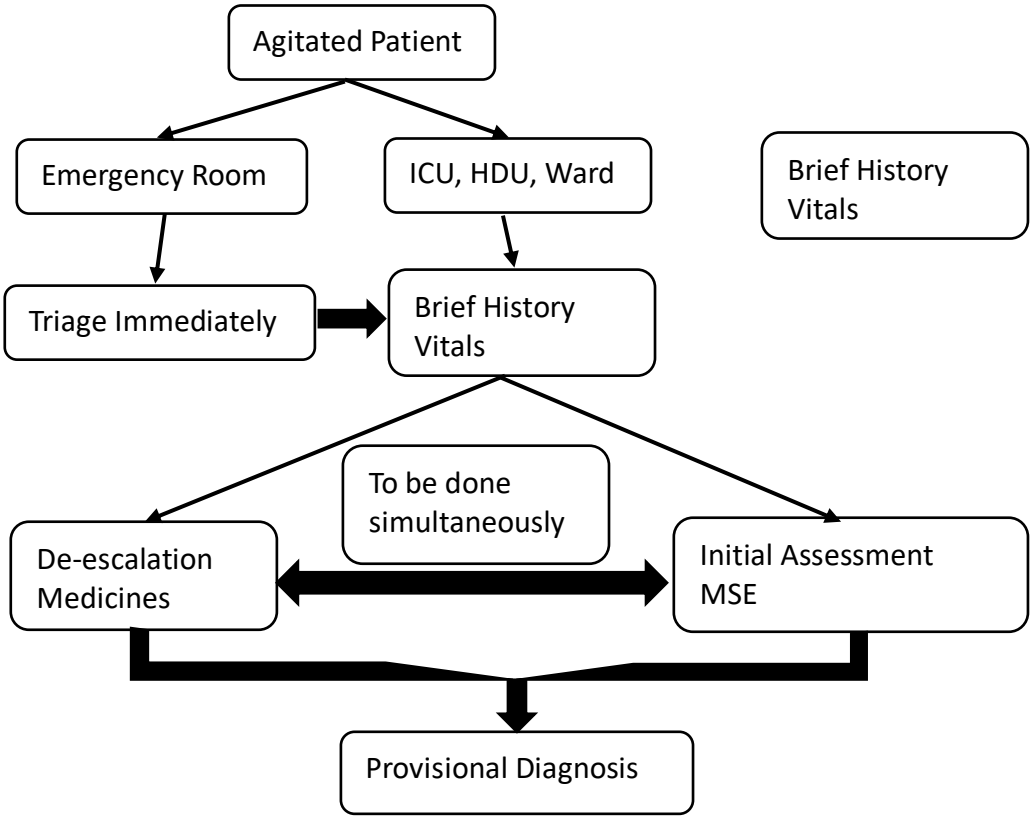
	No*	Yes	Time Resolved
Suspect New Onset Psychiatric Condition?	1		
Medical Conditions that Require Screening?	2		
Diabetes (FSBS less than 60 or greater than 250)			
Possibility of pregnancy (age 12-50)			
Other complaints that require screening			
Abnormal:	3		
Vital Signs?			
Temp: greater than 38.0°C (100.4°F)			
HR: less than 50 or greater than 110			
BP: less than 100 systolic or greater than 180/110 (2 consecutive readings 15 min apart)			
RR: less than 8 or greater than 22			
O_2 Sat: less than 95% on room air			
Mental Status?			
Cannot answer name, month/year and location (minimum A/O x 3)			
If clinically intoxicated, HII score 4 or more? (next page)			
Physical Exam (unclothed)?			
Risky Presentation?	4		
Age less than 12 or greater than 55			
Possibility of ingestion (screen all suicidal patients)			
Eating disorders			
Potential for alcohol withdrawal (daily use equal to or greater than 2 weeks)			
Ill-appearing, significant injury, prolonged struggle or "found down"			
Therapeutic Levels Needed?	5		
Phenytoin			
Valproic acid			
Lithium			
Digoxin			
Warfarin (INR)			

*** If ALL five SMART categories are checked "NO" then the patient is considered medically cleared and no testing is indicated. If ANY category is checked "YES" then appropriate testing and/or documentation of rationale must be reflected in the medical record and time resolved must be documented above.**

Date: _____ **Time:** _____ **Completed by:** _____ _____**, MD/DO**

Signature Print

Figure 2 Initial Assessment of Agitated Patient



(*) - Abbreviations

ICU - Intensive Care Unit
HDU - High Dependency Unit

Figure 3 Diagnostic Evaluation

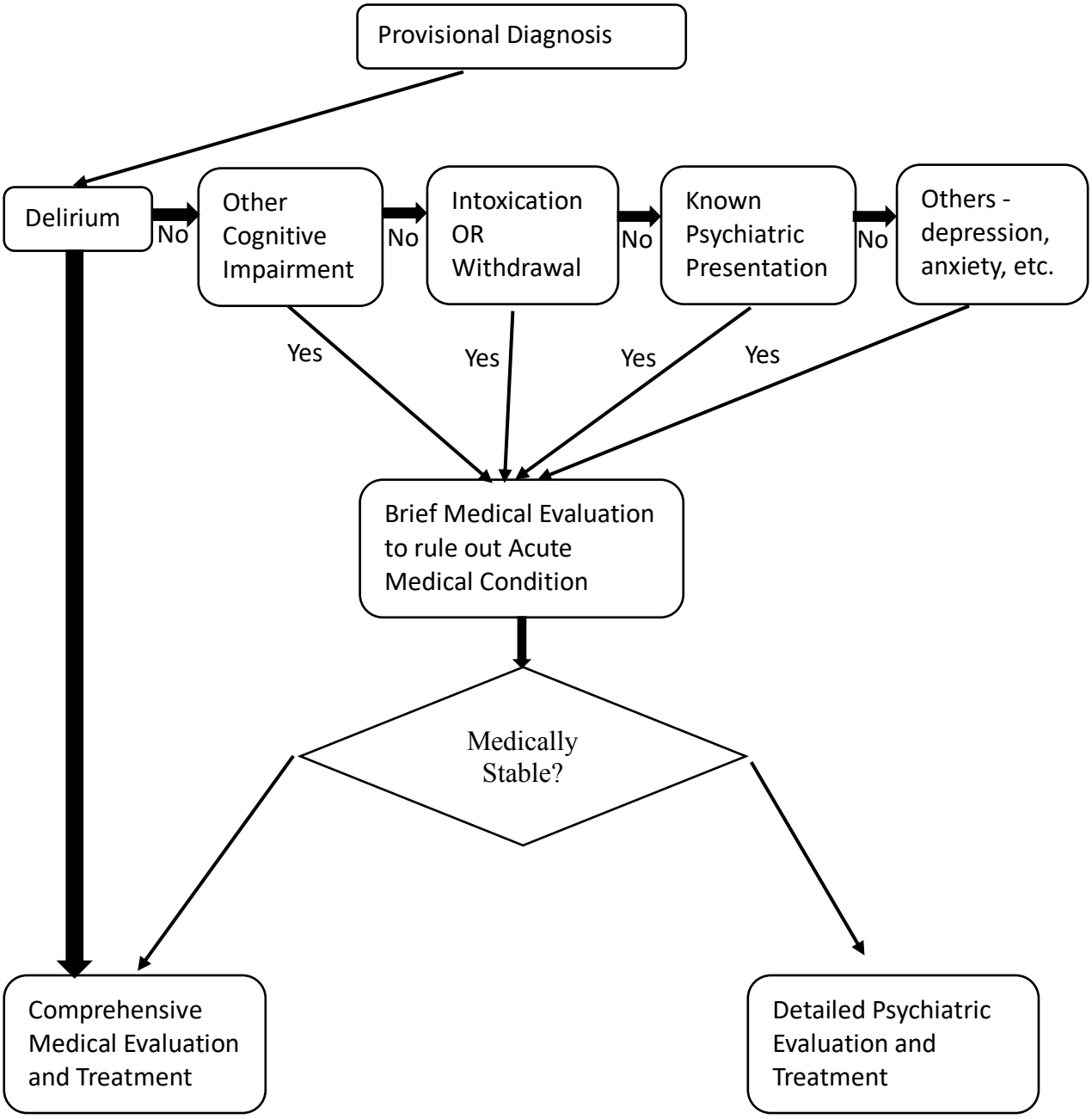


Figure 4 Algorithm to use Medical Restraint

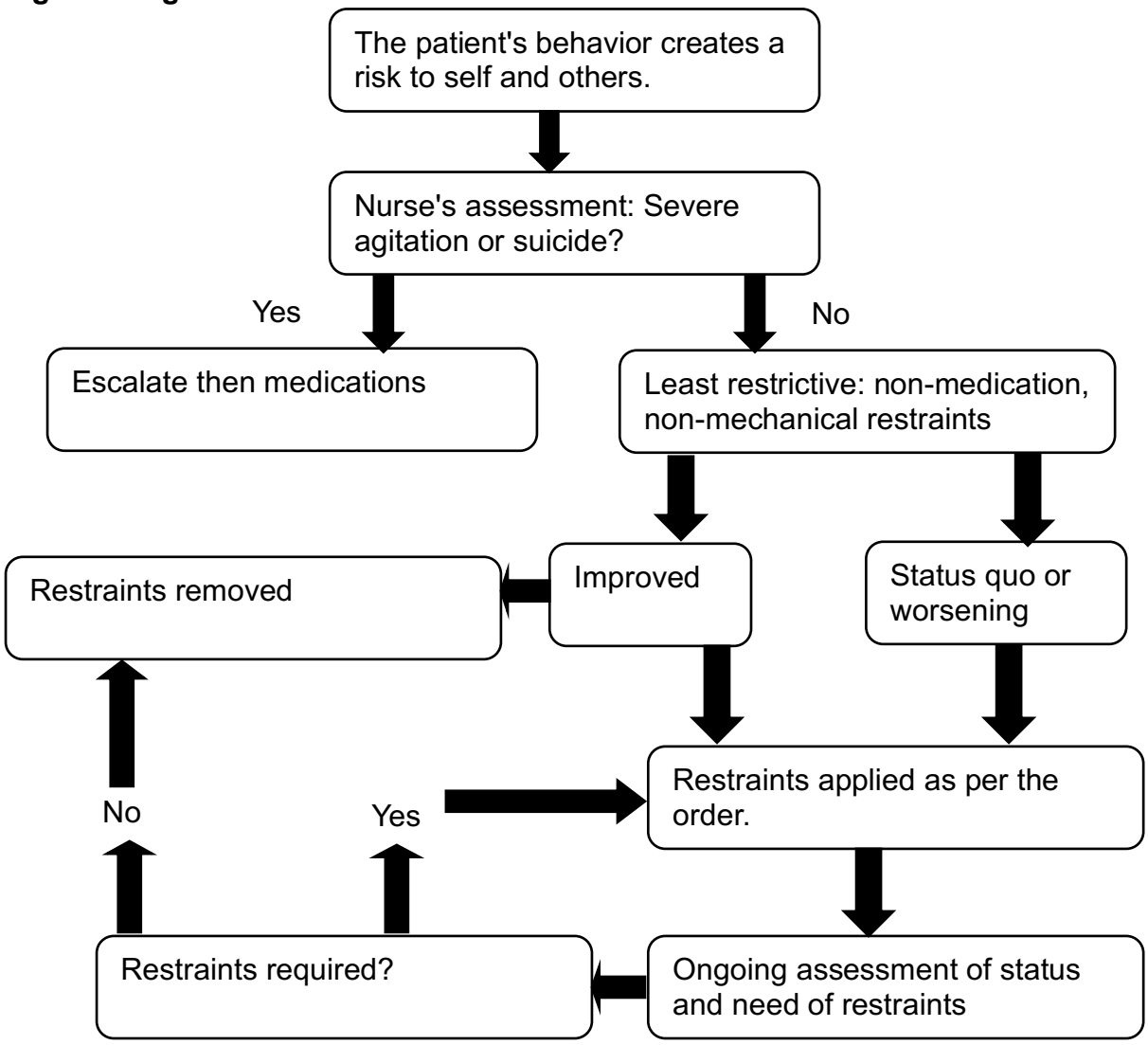
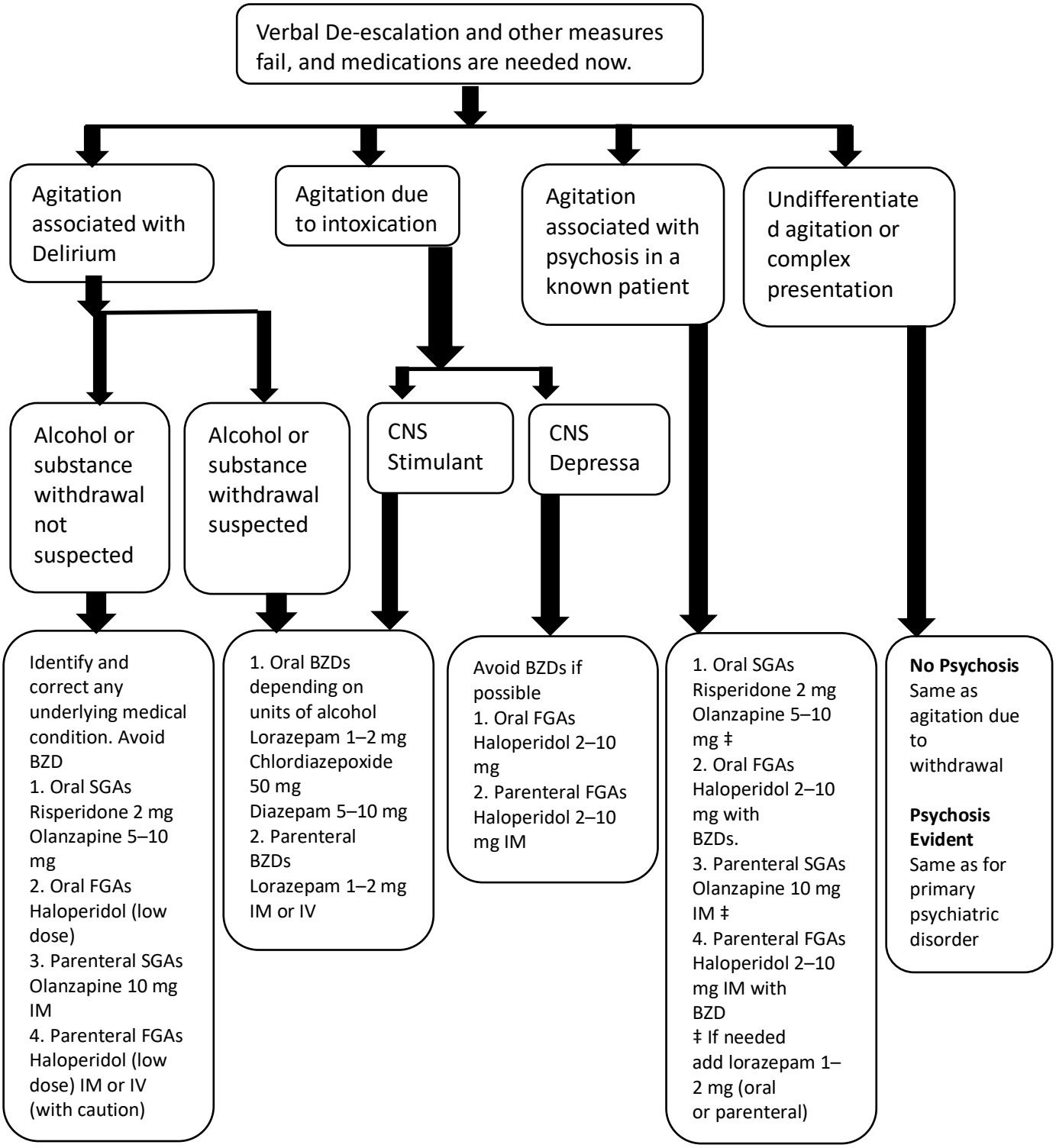


Figure 5 Pharmacological Intervention



Appendix 1

Medical Restraint Flowsheet

I. Patient's Details
Name: Age: Gender: M/F/O Hosp. No.

II. Clinician's Order
Name: Dr. Date: Time:
a) Doctor's Orders (Orders must be renewed every 12-24 hours based on the practice)
1.
2.
3.
b) Initial Order
Start: date/time
End: date/time
c) Repeat Order
Start: date/time
End: date/time

III. Alternatives attempted before initiation of medical restraints (check all that apply)
□ Re-orient patient to time/ date/place/person and/or situation
□ Move patient closer to the nurses' station
□ Conceal lines/ tubes/ devices
□ Minimize stimulation
o Reevaluate need for lines and tubes
□ Appropriate diversional activities
□ Repositioning
o Pain and sedation intervention
□ Other

IV. Indication for using medical restraints
□ Pulling lines
□ Pulling tubes
□ Removal of equipment
□ Removal of dressing
□ Inability to respond to direct requests or follow instructions
□ Other

V. Type and details of medical restraints applied (Tick all that applies)
Wrists: Both/Right only/Left only
Legs: Both//Right only/Left only
Gloves/Mittens: Both//Right only/Left only
Waist Belt: Yes/No
Side railings: Yes/No

VI. Psycho-education of the patient
a) Informed the patient about the need and alternatives for medical restraints. Yes/No
b) Periodically patient was explained about the behavior required to discontinue the restraint until an understanding was evidenced. Yes/No

Nurse's name & sign	**Date and Time**
Doctor's name & sign	**Date and Time**

Medical Restraint Flow Sheet contd…

VII. Patient's Monitoring Chart
In the first hour, observation checks are done every 15 minutes, then hourly
•15 minutes: Time_____ Behavior (**See Key)_____ Initials_____
•30 minutes: Time_____ Behavior (**See Key)_____ Initials_____
•45 minutes: Time_____ Behavior (**See Key)_____ Initials_____
•60 minutes: Time_____ Behavior (**See Key)_____ Initials_____

Time (Hours)	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	7
Observation check (**See Key) Q1h																								
Circulation/skin check Q2h																								
Food/ fluids Q2h																								
Elimination (or F for Foley in place) Q2h																								
Range of Motion Q2h																								
Change in type or number of Restraint (*See Key) Q1h																								
Staff initials																								

Key: *Restraints NC = no change ↑3=increase to 3pt ↑4=increase to 4pt ↓1=decrease to 1pt ↓2=decrease to 2pt ↓3=decrease to 2pt	****Observed Behavior (May use more than one)** **CF**=confused **AG**=agitated **VA**=verbally abusive **TF**=tearful **JC**=hallucination **DL**=delusional **A**=patient asleep **SD**=sedated **SB**=subdued **CA**=calm **CO**=cooperative **O**=other

VIII. Restraint discontinued:
Date: _____ Time: _____ □ n/a (ongoing)

Discontinue restraint at the earliest possible time that it is safe to do so, regardless of the scheduled expiration time of the orders.

Title: Assessment and Management of Agitation in Consultation-Liaison Psychiatry

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Appendix - 2

Abstract

Agitation is a commonly encountered emergency in emergencies, triages, and inpatient facilities. It is understood that as a continuum of a cluster of motor, verbal symptoms with emotional arousal range from mild to severe grade. The adverse outcomes of agitation like aggression, hostile, harmful, or destructive behavior, physical violence in consultation-liaison settings can, directly and indirectly, harm the established therapeutic environment and rapport with a patient. So, very early identification of agitation is necessary, as it is associated with high-risk aggression and violence. So, it becomes critical to evaluate and disseminate empirically derived best practices for assessing and managing agitation, which is socio-culturally acceptable for patients, caregivers, and healthcare staff, economically cost-effective to the healthcare system. This manuscript provides a detailed overview of etiology, assessments, approaches, and recent international accepted agitation management practice, suitable and legally accepted for Low- and Middle-Income Countries like India.

Key Words: Agitation; Assessment; Medical Restraint Order; Consultation-Liaison Setting; India.

Introduction to Agitation, Aggression, and Violence

Agitation is a heterogeneous concept, not only in terms of consensus of definition but also in management. It can be understood as a state of motor and cognitive hyperactivity, and it is characterized by inappropriate or excessive verbal or motor activity along with emotional arousal (Nordstrom et al., 2012). Garriga et al. defined agitation as “excessive motor or verbal activity, an emergent situation that is temporary, breaks the therapeutic alliance and requires a prompt and immediate intervention” (Garriga et al. 2016). The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines agitation as "excessive motor activity associated with a feeling of inner tension. The activity is usually non-productive and repetitious and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still” (DSM -5). Agitation is also a continuum of motor, verbal symptoms with emotional arousal, ranging from mild to severe (Zella et al., 2010). The different behavioural components of agitation are broadly divided into nonaggressive and aggressive behaviors, described in Table 1.

Table 1 Here

Due to the scarcity of systematic studies in this area, it will be challenging to look at the exact prevalence of acute agitation episodes; however, this remains a commonly encountered emergency in emergencies, triages, and inpatient facilities. The majority of agitation episodes in inpatient, outpatient, and emergency clinical settings varies. It ranges from 10.5% (Mellesdal, 2003) to 52% (Boudreaux et al., 2009) in the psychiatric inpatient setting. It may be more with emergency clinical settings. Ineffective early identification and management of agitation may unnecessarily warrant involuntary medication, physical restraint, and seclusion. This makes very early identification of rage in a clinical setting is necessary, as it is associated with high-risk aggression and violence. This is very important to ensure the safety of patients, families, and healthcare staff in a clinical setting. To assess and identify the agitation among the patient, there are well-developed standardized and applicable protocols and algorithms that can assist healthcare providers in identifying patients at risk of agitation (Garriga et al., 2016; Vieta et al., 2017). Further, Martínez-Raga et al describe the preliminary identification of agitation signs, which are all mentioned in the Table 2 (Martínez-Raga et al, 2018).

Table 2 Here

Identification and management of the agitated patient in consultation-liaison are critical, as it may not be equipped concerning trained healthcare professionals (HCPs), healthcare facilities, and the ethical/legal concerns on the different management procedures. Moreover, the adverse outcomes of agitation like aggression, hostile, dangerous, or destructive behavior, physical violence in consultation-liaison settings can, directly and indirectly, harm the established therapeutic environment and rapport with a patient. So, it becomes critical to evaluate and disseminate empirically derived best practices for assessing and managing agitation, which is socio-culturally acceptable for patients, caregivers, and healthcare staff, economically cost-effective to the healthcare system.

Etiology of agitation

Understanding etiopathogeneses of agitation, later risk, and vulnerability for physical aggression and violence is very important. The etiology of agitation can be understood in two broad subheadings, which are not mutually exclusive though:

a. Disease-related: Here, the cause of agitation is an identifiable disease, which can be a physical ailment or a mental health ailment.

a) Psychiatric manifestations of general medical conditions
b) Intoxication/withdrawal-related substance use
c) Primary psychiatric illness

b. Behavioural: Agitation is more of a person's behavior rather than a manifestation of an underlying physical or psychiatric illness. It is unlikely that this subgroup of patients will benefit from medical intervention (e.g., anti-social behavior, criminal behavior). In these conditions, a brief verbal de-escalation trial is considered. Subsequently, depending on the severity of agitation, security or law enforcement are considered. Other aetiologies have been mentioned in Table 3. In addition, the Individual characteristics that consistently increase the risk for physical violence among agitated patients in psychiatric inpatient settings are past episodes of aggression/violence, diagnosis of schizophrenia, presence of impulsivity/hostility, more extended hospitalization, involuntary hospitalization.

Table 3 Here

Assessment, Evaluation, and Approach to Agitation

Assessment and Evaluation of Agitation for medical, psychiatric causes are essential in a clinical setting. In the process of evaluation of an acutely agitated patient, healthcare staff must be prioritized these three aspects:

a. safety of the patient, caregivers, and healthcare staff
b. Immediate identification or exclusion of life-threatening medical and psychiatric conditions,
c. Consideration of a broad differential diagnosis to identify or exclude other common etiologies.

Amongst these, the safety of patients and staff remain at the top of the hierarchy. The different approaches should be tailored based on the patient's level of agitation and the level of threat that the patient poses. Despite this approach, one must remember that any patient is at risk for escalation, agitation, and violence under the right circumstances, irrespective of the initial degree of agitation. The clinician and staff can anticipate agitation/violence if warning signs (Table 4) are identified during the first assessment.

Table 4 Here

Universal safeguard measures to be observed during the initial evaluation include:

1. Routine, non-confrontational, and nondiscriminatory search and disarming of patients (ACEP, 1997)
2. Interviewing in a calm, quiet, private, but non-isolated setting (Rice & Moore, 1991; Tardiff, 1992)
3. Environment free of objects that could be used as weapons (Rice & Moore, 1991; Kuhn,1999)

Once arrangements are made for an ideal assessment environment and safety measures have been observed, the history and physical examination can be considered, which will guide the further evaluation and intervention process. Invariably, any agitation is prematurely attributed to psychiatric causes (anchoring bias) by clinicians, and this bias may potentially miss or ignore (confirmation bias) other significant findings that could indicate life-threatening illnesses or injuries (Sandu & Carpenter, 2006). So, history and physical examination help minimize bias in clinical decision-making. The main aim of this step is to exclude a medical/biological etiology of the patient's presentation and address it appropriately (Lukens et al., 2006; Tolia & Wilson, 2013).

If patients have a mild level of agitation but are cooperative, they can provide details of the circumstances of their presentation, including triggers and necessary interventions. If patients have a severe level of agitation and are uncooperative, then other resources such as friends or family members, attenders, nursing staff, documents can be the sources of information. Specific critical data must be obtained from the available sources as outlined in table 5.

Table 5 here

Meanwhile, investigations need to be evaluated if done already. Based on these, further inquiries can be asked for. The goal is to assess for medical causes of agitation.

Laboratory investigations are asked for:

- Random Blood Sugar Level, Fasting Blood Sugar Level, Post Prandial Blood Sugar Level, Complete Hemogram, Renal Function Test, Liver Function Test, Thyroid Function Test, Urine complete routine, microscopy, Urine drug screening, and serum Toxicology assay as per the presentation of the case or case to case basis

- Drug levels: if patients are on valproate, lithium, carbamazepine medications.

- Ultrasonogram (USG) of body parts interested on a case-to-case basis.

- 12 lead ECG

- Imaging: Computer Tomography (CT) brain or area of interest or Magnetic Resonance Imaging (MRI) Brain or area of interest as per the presentation of the case.

- Lumbar puncture and Electroencephalogram (EEG) as and when indicated.

4 - Differential Diagnosis of Acute Agitation

An acutely agitated patient may present anywhere along the spectrum from non-agitation (average level of activity) to severe agitation. In addition, this level of agitation is often dynamic in response to stimulations and interventions (verbal de-escalation or medications). Standard Differentials that can be considered are outlined in table 6.

SMART Medical Clearance Protocol (SMART)

Standardized screening protocols have been developed to guide the focused medical assessment and implemented in some settings and are helpful for quick decision making. One

such protocol is by Dr. Seth Thomas and colleagues known as SMART Medical Clearance Protocol (SMART), shown in figure 1. This can be customized to address the local clinical needs in practice.

Figure 1 SMART Medical Clearance Form here

Psychiatric Evaluation of Agitation

The psychiatric evaluation of agitation goes hand in hand with medical evaluation. Therefore, the psychiatric and medical assessment plan will be the same, including Initial exploration – history of present illness, Psychiatric status examination (PSE), Working diagnosis, differential diagnosis, Risk assessment, Completion of psychiatric history, and any definitive diagnosis. Therefore, the evaluation algorithm is given in figures 2 and 3.

Figure 2 & 3 here

Intervention

As a first thing to do, the psychiatrist should discuss with referring unit /clinician and explain/educate about the need of:

- Intervention goals are from the individual patient's perspective
- Need of a structured setting to ensure proper evaluation/interventions
    - Privacy: room (private/semi-private)
    - A realistic and clear set of expectations with a written schedule
    - Staff who is responsible for the individual patient's care
- Attempting to enlist the patient in the treatment, i.e., past good response to the type of medication, total dose received side / adverse effects, and route of administration.

Goals of Intervention

The safety of patients and others is the first goal. In the process, other plans to be achieved are collections of samples for laboratory evaluations, establishing rapport, arriving at a provisional diagnosis, facilitating the resumption of treating team-patient relationship, calming the patient without sedation, and co-management with a medical /surgical team. Few general recommendations to be followed in managing agitation are outlined in table 7.

Table 7 here

Agitation Management

The management of agitation begins during the evaluation process itself; instead, both will be happening simultaneously. The steps in the direction of agitation can be as follows ((Hollman & Jeller, 2012)

- Medical evaluation and triage
- Psychiatric evaluation
- Verbal de-escalation and Communication/Behavioral Interventions (table 8)
- Environmental interventions
- Psychopharmacologic interventions
- Use of seclusion/restraint
- Co-management with medical /surgical team

Table 8 here

Environmental Interventions

Environmental interventions will focus on decreasing the sensory stimulation of the patient and providing a safe environment to the patients, which will aid the clinician in clinical observation in ensuring the safety of the patient and the healthcare workers. Examples include: clearing the room, removing any dangerous objects, having staff available as a "show of force," close observation, calm conversation, reducing the sensory stimulation.

Medical Restraints

Medical restraint and seclusion have been part of the medical and psychiatric settings for ages. The current practice of using medical restraints has deep roots in history and has evolved in legal frameworks. Written informed consent from patient and family member or only family member/legal guardian, if the patient is unable to consent, must be taken in the presence of two witnesses. The duration of medical restraint should be explained. This should be done every time restraints are used. It is important to note that medical restraints should not be used for the purposes like punishment or as a form of discipline, as a substitute to less restrictive measures, as a precaution when there are inadequate nursing/healthcare workers.

To determine when medical restraint can be used, local algorithms can be developed as per the institution's need. A sample algorithm is shown in figure 4. Indications and contraindications for medical restraints have been mentioned in the tables 9. Adverse outcomes related to restraints have been mentioned in table 10.

Tables 9 &10 here

Figure 11 here

Alternative medical restraints: physical, chemical, environmental, and seclusion.

Physical: These include hand straps, limb ties, belts, straitjackets, fabric body holders, four-point restraints, tucked tightly in bedsheets, bedside rails, mittens/gloves to prevent scratching. Factors to be considered before using the physical constraints are detailed in table 11.

Table 11 here

Chemical: These include mainly antipsychotics and benzodiazepines, administered either orally or parenterally based on the severity of agitation. Usually, these may not be a part of a patient's ongoing treatment regimen, and these are used with the only purpose of restricting the patient's behaviour.

Environmental: This includes preventing free movement of the patient on a premise to ensure the safety of the patient and others. This can be a closed ward.

Seclusion: This includes placing the patient alone in a room or an area with the doors closed to prevent exit from that place.

Medical Restraint Order

Medical restraint order must be written clearly, and it should include: the reason for the restraint, duration of the medical restraint, type of restraint, monitoring schedule when to discontinue. In addition, the patient's basic needs to be attended to nutrition, hydration, elimination, hygiene, range of motion, circulation. Further, the file should have the following documentation: clinician's order, an initial assessment by the resident doctor/duty doctor and in-person evaluation by the consultant as early as possible, alternatives which were considered and tried, monitoring of patient and outcomes of interventions used, periodic re-assessments for vitals and progress of agitation and physical condition, psychoeducation of patient and family member about the medical restraint provided.

Instructions to the staff carrying physical restraint

The team who will take physical restraint should be given clear instructions as detailed in table 12.

Table 12 here

Documentation during restraint

For adequate and better quality of care, accurate and detailed documentation of restraint episodes is essential. It will begin with the reason for restraint and informed consent of the patient and family member/legal representative. The documentation should include behaviour that necessitates the continued need for medical restraints, mental status of the patient, details of medical restraints used and location of restraints, vitals, airway/breathing/circulation, condition of limbs, range of motion in limbs, notes on skin care-change of posture, sponge bath, etc., liquids, food, and toileting offered. A sample medical restraint flowsheet is in Appendix 1.

Alternatives to restraint

Downey and colleagues (2007) noted that about 90% of the emergency departments consider using an alternative before actually restraining. One-to-one verbal dialogue is the most commonly used method, followed by the time-out or pastoral care method. Three standard options suggested by Konito et al.,

1. Nursing interventions – The mere round-the-clock presence of the nursing staff and regular staff conversations with the patients will keep them engaged, and the chances of aggression decrease.
2. Multi-professional agreements involving patients – It was noted that deals involving physicians, nursing staff, and the patients about the medications, dosage, difficulties in the ward, and criteria for restraint and seclusion would make the patient participate in the treatment process, and turn, more cooperative and less aggressive.
3. Use of authority/power, either in the form of strength of the ward staff or in the form of a person with authority, like the clinician or a senior nurse –presence or a conversation with the authority will aid in controlling the aggression without the need for restraint.

Pharmacotherapy

Despite these interventions, the patient makes further threats, throws objects, starts to pace, makes gestures to hit, then pharmacotherapy is used. However, preparation for pharmacotherapy should be ready all the time. A crash cart in each hospital ward should have the psychotropics required for sedation. Before the beginning of the assessment, security guards should be informed to be ready to assist immediately.

Goals of Pharmacotherapy

- Ideally, pharmacotherapy for acute agitation should:
  - Be non-traumatic and easy to administer
  - Have a rapid onset of action (rapid tranquilization) and for a sufficient duration without excessive sedation
  - Have a minimal or low risk for significant adverse events and drug interactions

- Psychopharmacologic treatment endpoint should be **rapid tranquilization** (Vieta et al., 2017)
  - Calming process separate from total sleep induction

- Allows the patient to participate in the care
- Helps the clinician to collect history, start a work-up, and initiate the treatment of unidentified conditions
- Better therapeutic endpoint
- Sleep induction is not the desired outcome
    - It conflicts with the goal of participation by the patient
    - It may not be essential for the improvement in the agitation or decrease in the psychotic symptoms

Pharmacologic Considerations

The medications used for the management of agitation should be available in crash court. These should be easily storable. The rapidity with which these can be reconstituted and administered will help. Further, the onset of action of these medications should be rapid. The same medicine may act rapidly when the parenteral route is preferred. The decision regarding the route of administration has to be made by the treating team based on the severity of the agitation. In general, intravenous administration will deliver the medications rapidly, and the onset of action will be faster than when medicines are administered via the intramuscular or oral route. So, in cases of severe agitation, intravenous preparations are preferred. Once issued, the medication should exert its' effects for sufficient duration. The administered drug should have minimal adverse effects and minimal or no interactions with other medicines. The factors to be considered while choosing medications areas are in table 13.

Table 13 here

Association for Emergency Psychiatry Recommendations

- Undifferentiated Agitation/Suspected intoxication with stimulant or withdrawal from alcohol/benzodiazepine
    - Oral benzodiazepines (e.g. lorazepam 1-2 mg)
    - Parenteral benzodiazepines (e.g. lorazepam 1-2 mg IM or IV)
    - Acute intoxication with Central Nervous System (CNS) depressant (e.g., alcohol)

- Avoid benzodiazepine if possible
- Oral 1st generation antipsychotic (e.g. haloperidol 2-10 mg)
- Parenteral 1st generation antipsychotic (e.g. haloperidol 2-10 mg IM)

- Delirium (not associated with alcohol or benzodiazepine withdrawal)
  - Oral 2nd generation antipsychotic (e.g., risperidone 2 mg, olanzapine 5-10 mg)
  - Oral 1st generation antipsychotic (e.g., low dose haloperidol)
  - Parenteral 2nd generation antipsychotic (e.g., olanzapine 10 mg IM)
  - Parenteral 1st generation antipsychotic (e.g., haloperidol low dose IM or IV)

- Schizophrenia or Mania
  - Oral 2nd generation antipsychotic alone (e.g., risperidone 2 mg, olanzapine 5-10 mg)
  - Oral 1st generation antipsychotic (e.g. haloperidol 2-10 mg with benzodiazepine)
  - Parenteral 2nd generation antipsychotic (e.g., olanzapine 10 mg IM)
  - Parenteral 1st generation antipsychotic (e.g. haloperidol 2-10 mg IM) along with benzodiazepine (e.g. lorazepam 1-2 mg)

Emergency Psychiatry / Agitation Pharmacological Preparation Silent information

- **Benzodiazepines**
  - Benzodiazepines (BZDs) act by facilitating the activity of GABA
  - GABA is a major inhibitory neurotransmitter
  - Therapeutic effects appear linked to decreased arousal
  - Little benefit for psychiatric symptoms other than anxiety
  - A long history of use in the management of acute agitation
  - Individually
  - Combination with antipsychotics (*except* IM olanzapine)
  - Preferred in a patient in whom agitation is secondary to alcohol or sedative withdrawal
  - Lorazepam
    - Only benzodiazepine with complete and rapid IM absorption

        - No involvement of P450 system
        - IM or sublingual administration
        - 60-90 minutes until peak plasma concentration
        - 8-10 hour duration of effect
        - 12-15 hour elimination half-life

    - Side effects
        - Excessive sedation
            - Additive with other CNS depressants
        - Respiratory depression
            - BZDs avoided in patients at risk for CO_2 retention
        - Paradoxical disinhibition
            - More likely with high doses in patients with structural brain damage, mental retardation, or dementia
        - Ataxia

- **Typical Antipsychotics**
    - Dopamine antagonist
        - Positive
            - Antipsychotic
            - Anti-agitation
        - Negative
            - Extrapyramidal symptoms (EPS)
            - Neuroleptic Malignant Syndrome (NMS)
    - Many authors consider typical antipsychotics the treatment of choice in acute agitation, especially in the setting of delirium.
- Low potency
    - Not recommended
- High potency - **Haloperidol**
    - Virtually no anticholinergic properties
    - Little risk of hypotension
    - It does not suppress respiration
    - Can be given IV
    - Fast-acting

        - The onset of action: 30 minutes
        - Duration of action up to 12-24 hours
- Side effects
    - Extrapyramidal symptoms
        - Dystonia
        - Akathisia
        - Parkinson-like effects
    - QTc prolongation
        - Rare at low doses
    - Lower seizure threshold
        - Low-potency > high-potency antipsychotics

- **Atypical Antipsychotics**
        - Broader spectrum of response
        - Different side effect profile
            - Fewer EPS and akathisia
            - QTc concern remains
            - Metabolic syndrome
    - Olanzapine
        - Intramuscular
        - Oral tablet
        - Oral tablet, disintegrating
    - Aripiprazole
        - Oral solution
        - Oral tablet
        - Oral tablet, disintegrating
    - Risperidone
        - Oral solution
        - Oral tablet
        - Oral tablet, disintegrating
    - Quetiapine
        - Oral tablet
    - Ziprasidone
        - Intramuscular

        - Oral tablet
    - Olanzapine
        - IM dose range of 5-10mg
        - Maximum of 30mg/day
        - 15-45 minutes until peak plasma concentration
        - 21-54 hour elimination half-life
    - PO dose range 5-10mg
        - Flexible dose up to 40 mg/day better than fixed 10 mg/day dose
        - 24-54 hour elimination half-life
        - 1-3 hours until peak plasma concentration, but benefits often occur in less time
    - Adverse events
        - Concern of orthostasis
        - Long-term use has been associated with the development of metabolic syndrome.

- **Risperidone**
    - 2 - 6 mg PO or ODT
    - Oral risperidone concentrate 2mg + oral lorazepam 2mg equivalent to IM haloperidol 5mg + IM lorazepam 2mg
    - Oral risperidone 2 mg is equally effective as oral haloperidol 5 mg
    - Overall not thought to be superior to other antipsychotics

- **Aripiprazole**
    - It is unique in that it is a partial dopamine agonist
        - Decreases dopamine in hyper-dopaminergic areas of the brain
        - Increases dopamine in hypo-dopaminergic areas of the brain
    - Oral aripiprazole 15 mg as effective as oral olanzapine 20 mg
    - Low risk for QT interval prolongation (<1%)

- **Quetiapine**
    - 25mg onwards up to 400mg
    - 1-3 hours to peak plasma concentrations
    - Shallow risk of EPS

- Sedation and orthostasis are side effects

Combination Therapy

- Individual medications can be targeted to the different components of agitation.
  - Anxiety and arousal → benzodiazepine
  - Psychosis → antipsychotic
- Combining medications at low doses may reduce individual side effects (decrease Cmax) while obtaining the desired result.

- Most common combination
  - Haloperidol 5mg IM
  - Lorazepam 2mg IM
  - Benefits
    - Faster reduction in agitation
    - Fewer injections required
    - Simple to administer
    - Lower incidence of EPS
- Side effects
  - Overall, very well tolerated
  - Side effect profiles of both the BZDs and antipsychotics apply
  - Excess sedation most common adverse reaction
    - However, recent studies suggest sedation rates appear similar to lorazepam treatment alone.

Special Population: ICU patients

- Mechanically ventilated ICU patients: analgesia and sedation are recommended
- Atypical antipsychotics may decrease the duration of delirium in ICU patients.

Special Population: Weaning of Ventilation

- Dexmedetomidine (alpha two adrenergic sedatives)

- Better than midazolam (hypertension and tachycardia, time intubated)[1]
- Better than haloperidol (time intubated, length of stay)

The role of Benzodiazepines and Antipsychotics has been described in tables 15 and 16.

Table 14, 15 & 16 here

Figure 5 here

Conclusion

This review provides a detailed overview on etiology, assessments, approach and recent international accepted agitation management practice, as well as a pragmatic guide for clinicians who treat agitation in the inpatient psychiatric and consultation-liaison setting. The internationally accepted agitation management practice recommends that agitation be recognised early with warning signs, starting with nonpharmacological interventions to deescalate the patient's agitation. If these measures remain ineffective, guidelines recommend administering medical restraint to calm patients rather than overly sedating them rapidly. Therefore, the clinician has to make a call to choose medical restraint order, which is non-invasive and easy to administer, has a rapid onset, effectively calm without excessively sedating the patient, and addresses patients' agitation. In addition to medical restraint orders and alternatives, medical staff needs to be trained through a mock drill to ensure best practice. Along with that documentation and monitoring of the continued need for medical restraints, mental status of the patient, details of medical restraints used and location of restraints, vitals, airway/breathing/circulation, condition of limbs, range of motion in limbs among patients on medical restraint order and the alternative is essential to ensure the adequate care and follow the best practice, which is socio-culturally acceptable, suitable and legally accepted for Low- and Middle-Income Countries like India.

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MANAGEMENT OF PSYCHIATRIC DISORDERS IN PATIENTS WITH CARDIOVASCULAR DISEASES

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Introduction

Cardiovascular diseases, and Psychiatric illnesses run in a chronic course and both have high morbidities and impaired quality of life apart from higher mortality than general population. Cardio metabolic syndrome is approximately 1.5-2 times higher in people having severe mental disorders like Schizophrenia and Bipolar disorder.[1] Mostly due to poor insight and lack of physical exercises, individuals with psychiatric disorders are at high risk of chronic obstructive airway diseases, tuberculosis, respiratory tract infections and other respiratory illnesses, obesity, diabetes and other lifestyle diseases compounded by psychoactive substances use further increasing the complexity.

Introduction:

Psychiatric illnesses and Cardiovascular disorders are the leading causes of morbidity and mortality among the global population. Cardiovascular disorders (CVDs) are the leading cause of death according to the World Health Organization, representing 32% of all deaths globally(1). About 970 million people are affected with mental illness throughout the world. Psychiatric disorders are one of the leading causes of morbidity across the globe (2).
The relationship between mental illness(MI) and CVD is a complex one, with no clear cause and effect. Both have many similarities. Like cardiovascular diseases, mental illnesses also run a chronic course. Both have higher rates of morbidity, mortality, and impaired quality of life when compared to the general population.

Cardiovascular disease has been found to be approximately 1.5-2 times higher in people having severe mental disorders like schizophrenia and bipolar disorder(3). Individuals with psychiatric disorders are also at risk for chronic obstructive airway diseases, tuberculosis, respiratory tract infections and other respiratory illnesses, obesity, diabetes and other lifestyle diseases compounded by psychoactive substance abuse, especially nicotine. Poor insight, poor access to healthcare services, lack of social support, stigma about psychiatric illness even amongst physicians often lead to insufficient screening for physical health in these patients. Commonly used psychiatric medications such as lithium, sodium valproate, olanzapine, clozapine, risperidone

etc are known to cause weight gain and also increase the risk of metabolic syndrome and consequences thereof(4).

The CVRF (Cardiovascular risk factors) are on rise in general population and poor control of these CVRF are responsible for poor health related quality of life (HRQOL).The self and perceived stigma are high among both mentally ill patients and their clinicians (both liaison physicians and psychiatrists).The integration of mental health care with other specialities and screening of cardiovascular risk factors starting from primary care level should be the call for the day. Many a time the treating doctor don't pay due to attention to their patients suffering from cardiovascular disorder which is generally observed as afinding as underdiagnosing the underlying cardiovascular disorders is afinding in literature.. Pharmacoeconomics also contributes as a key role for the reason of poorer management of cardiovascular risk factors among mentally ill persons.[4]

From the Cardiological view side, it has been consistently found that the prevalence of psychiatric disorders in liaison psychiatry is very high ranging from 48-87% across cardiovascular, musculoskeletal and orthopedic patients(5). Following adverse coronary events, many people do suffer from depression, anxiety, acute and post traumatic stress disorders which can have negative impact and further consequences leading to heart failure, stroke and acute myocardial infarction(6) thus increasing the cardiological morbidity and contributing to the mortality as added risk of psychiatric morbidity.

We will now look at individual psychiatric disorders and their relationship with CVDs. Management AND suggested guidelines will run along the lines of safety and efficacy profiles in this population of patients.

Again the chronic psychotic disorder Schizophrenia patients do have higher than general population risk of hypertension, coronary vascular disorders, myocardial infarction and higher incidences of sudden unexplained death due to cardiac reasons. The causes obviously are attributable to multifactorial genetics, metabolic parameters, prominent among them is insulin resistance ,obesity, less physical activity and due to medication used in management of chronic psychotic disorders.

When cardiac medicines and psychotropic medicines are given together (like antihypertensives and psychotropic medicines), there is high chance of causing severe hypotension. Many psychotropic medicines alter the cardiac conduction with prolongation of PR, QRS and QTc intervals, ST segment depression, decrease T wave amplitude and large U waves in ECG. This effect is potentiated by synergistic effects of antiarrythmic drugs. SSRIs can displace other protein bound drugs and may lead to toxicity. Hence dual patientswith both cardiovascular and psychiatric morbidities need to be watched as suggested guideline for drug-drug interactions and pharmaco kinetics too as abundant precaution to check for the medicines patient are already taking and which best to add in these patients.

Table 1 *: **Salient points about relationship between Coronary Artery Disease and psychiatric disorder.***

CVDs are the leading cause of death globally (17.7 million, 31% Of all deaths worldwide).
300 million people are suffering from mental illnesses & CVD will be the leading cause of disability worldwide by 2030 (14.3 millions of all deaths).
Depression is an independent risk factor of CAD and carries a bidirectional relationship.
Post MI depression has 1.6-2.7 fold increase risk of mortality.
The cardiovascular mortality gets almost doubled in persons suffering from Bipolar disorder (RR 1.5-2) than the general population.
Stress, anxiety, panic disorder, post traumatic stress disorders etc increases mortality in persons having cardiovascular disorder (RR 2.0-4.0).
Development of PTSD (Post traumatic stress disorders) in persons having ACS (Acute Coronary Syndrome) increases the risk of relapse of ACS (RR=2.0) in 1-3 years time.
HPA axis dysregulation, raised serum cortisol and failure of non suppression in DST (dexamethasone suppression test) have been found in PTSD and other anxiety disorders which substantiate the causal relationship.

Mood disorders and cardiovascular disorders:

Depressive disorders:

Depression and cardiovascular disease have a bidirectional relationship. Depression has been consistently linked to CVD as a risk factor(7). Depression is seen in 15-20% of patients with coronary artery disease(CAD). These rates are higher in patients with myocardial infarction(MI), with upto two-thirds of the patients having some form of depression either during hospitalisation or in follow-up(8). 15% of patients undergoing CABG have depression meeting diagnostic criteria. Women have a higher risk, almost two fold, when compared to men especially in those younger than 60 years(9). It is also found in 20% of patients with congestive heart failure with higher rates in more severe patients and as well as peripheral artery disease(8,10,11). Around 30% of implanted cardioverter defibrillator recipients have been found to have anxiety(12).

Table 2: Several biological mechanisms have been suggested to explain the underlying relation between depression and Cardiological disorders ..

S.No	Biological mechanisms
1	Autonomic dysfunction - Depression has been found to be associated with decreased heart rate variability, resting tachycardia, hypertension, left ventricular hypertrophy, arrhythmias, mismatch in myocardial supply and demand, reduced baroreceptor sensitivity.
2	Inflammation and impaired immunity - Depressed patients have been found to have higher production of interleukins 1 and 6, tumour necrosis factor(TNF)-alpha, alpha interferon, C-reactive protein which may heighten risk for CVDs.
3	Neuroendocrine homeostasis - Both internal and external environmental stressors have been found to have an effect on the neuroendocrine system leading to changes in synthesis and use of serotonin, dopamine, norepinephrine. Abnormal activation and feedback of the hypothalamic-pituitary-adrenal(HPA) axis leads to dysregulated response of corticotrophin releasing factor(CRF) and adrenocorticotropic hormone(ACTH) thus leading to hypercortisolemia.
4	Endothelial dysfunction - There are increased levels of soluble VCAM-1, VWF and circulating CEC leading to endothelial damage and reduced endothelial NO synthase– and COX-independent relaxation leading to atherosclerotic changes in the vessels.

5	Impaired platelet functioning - Increased platelet reactivity is seen due to increased platelet aggregation, elevated platelet thrombin response, and elevated levels of platelet factors. Increased platelet reactivity in depression can also be seen due to exaggerated serotonin response, reduced serotonin transporter binding, decreased platelet serotonin levels, and high platelet serotonin density.
6	Insulin resistance - Depression may lead to immune regulated destruction of the pancreatic beta islet cells leading to increased insulin resistance which is a risk factor for CVD.
7	Genetic factors - Family history plays a major role in both depressive and cardiac illnesses. Genes identified to have a common link between the two disorders include BDNF, MTHFR, CACNA1D, CACNB2, GNAS, ADRB1, NCAN, TLR4, REST, FTO, POMC, CREB, ITIH4, LEP, GSK3B, SLC18A1, ADRA2A, PPP1R1B, APOE, CRY2, HTR1A, TCF7L2, MTNR1B and IGF1. These genes have been implicated in neuroendocrine and HPA axis systems.
8	Lifestyle and behavioural factors - Decreased physical exercise, poor nutrition, substance use, non-compliance to medication play a role in worsening cardiovascular status.

Depression and cardio vascular disorders

Depression is often found to be persistent and recurrent in these patients. Studies have found that depression is often present before the incident cardiovascular disease presentation and is a major factor for poor outcome(16). It was also seen that during follow-up following a cardiovascular episode, depression was found to be chronic or relapsing in almost half the patients diagnosed with major depression at the incident episode. 40% of the patients who had minor depressive symptoms progressed to have major depressive episode within 1 year(17,18). At least 65% of patients with MI report depressive symptoms while 20% of them fulfill criteria for a major depressive episode(19-21).

Co-morbid anxiety disorders have been found to co exist with depressive disorders in at least 40% of the patients diagnosed with depression. Most common anxiety disorders include generalised anxiety disorder(GAD) and post-traumatic stress disorder(PTSD). These worsen the outcome for both depression and cardiac disease(22).

Screening for depression can be done using scales such as Public Health Questionnaire-9(PHQ-9)(23), Beck Depression Inventory(BDI)(24), Hamilton Rating Scale for Depression(HAM-D)(25). Cardiac Depression Scale(CDS)(26) has been developed for screening and measurement of severity of depression in cardiac patients specifically(19,27)., hence practically whenever it is possible to use the rating scales is advisable .

Treatment of depression in coexisting cardiovascular disorders :

Many studies have been done which have looked at treatment of depression in cardiac patients. The prominent and significant among them are the following studies SADHART(28) and UPBEAT(29) studies have looked at the efficacy of sertraline while MIND-IT(30) studied the effects of mirtazapine and citalopram. ENRICHD(31) and CREATE(32) studies looked at the efficacy of CBT and IPT along with pharmacological treatment. Most studies have found only a small to modest effect in cardiac outcomes in patients treated with proper antidepressants or psychological therapies. However, outcomes related to depression were significant, i.e, patients improved significantly following the interventions. Reduced morbidity and mortality in psychiatric patients has been documented to some extent in these studies.

Table 3 : Summary of evidence of Pharmacological management of depression :

Class of antidepressants	Safety and efficacy profile
SSRIs	These have better safety profile than other classes. Sertraline, escitalopram, fluoxetine have been found to be safe and efficacious. Citalopram can cause prolonged QT interval and should **be preferably avoided.**
SNRIs	They have a small but definite risk of hypertension, tachycardia, and orthostatic hypotension**. To be used with slight caution**.
Newer/atypical antidepressants(fewer studies, so data should be interpreted with caution)	Bupropion - No significant adverse effects. Mirtazapine - Increased appetite may lead to obesity and hyperlipidemia which is a risk factor for CVD. Otherwise, Mirtazapine is found to be efficacious. Risk of TdP is not found to be significant. Vilazodone - Research reports of palpitations but no other significant cardiac adverse effects. Agomelatine - No significant adverse effects Vortioxetine - No significant adverse effects found yet Buspirone - No significant adverse effects at therapeutic doses Nefazodone, Trazodone - May cause prolonged QT interval, orthostatic hypotension **to be avoided**

TCAs	May cause prolonged QT interval, arrhythmias, severe orthostatic hypotension, sinus tachycardia, may predispose to heart blocks. To be avoided/used with extreme caution. **(to be avoided**)
MAOIs	Tachycardia, hypotension, hypertensive crisis with tyramine rich foods, prolonged QT interval are seen with administration of MAOIs. **To be avoided**.

******(SUMMARISING FROM ENHANCE STUDY, SADHART AND CREATE STUDIES)**

Psychological treatment in depression with cardiovascular patients:

Quality studies are by far less and in between. Stress management techniques, relaxation techniques, CBT have been found to be beneficial when compared to placebo in these patients though the sample size and methodology in these studies are not very rich and sound. They have been found to improve the quality of life. ENRICHD(31) and CREATE(32) studies looked at the efficacy of CBT and IPT along with pharmacological treatment . It is thus suggested that patients with cardiovascular disorders psychotherapies are suggested guidelines.

Bipolar disorder(BPAD) and cardiovascular disorders :

CVD is the leading cause of death in patients with BPAD, with 35-40% of deaths accountable to it(38). The rates of bipolar patients having CVD is 2-3 times more than compared to the general population(39). This decreases the life-span of patients by 10-15 years when compared to the general population. The elevated risk of CVD has been found even in absence of poor lifestyle factors, substance use, and use of medication. The risk is higher in the younger subset of patients when compared to other age groups and the population. Meta-analytic studies showed a hazard risk ratio of 1.54 for CAD and 2.1 for CHF in bipolar patients when compared to control subjects(40,41).

The medications used to treat bipolar disorder includes mood stabilisers such as lithium, Divalproex and antipsychotics, especially second generation antipsychotics namely Olanzapine, Clozapine,Risperidone etc have a propensity to cause weight gain, impaired glucose tolerance, hyperlipidemia, obesity and metabolic syndrome which are independent risk factors for CVD(42). Behavioural factors such as poor nutrition, substance use, poor compliance to treatment, impaired sleep also play a role in elevating risk for CVD. All these factors need to be taken into the picture in planning management of CVD in bipolar patients.

There are common biological links underlying the two disorders that provide some explanation to the relationship between the two (43, 44).
There are many biological theories existing to explain the basis of both cardiological disorders and depression. Some of the theories do have a commonality for both disorders.

Table 4: Showing the suggested biological basis for cardiovascular and depression

S.No	Biological mechanisms
1	Inflammation - Inflammatory markers such as IL-6, CRP, TNF-alpha have been found to be raised during symptomatic episodes of the disorder and also are implicated in atherosclerosis.
2	Oxidative stress - Oxidative stress has been seen in BPAD in frontal regions of the brain especially during the mood episodes. Mitochondrial dysfunction has also been implicated. Oxidative stress has a role in endothelial dysfunction, thus creating a link between BPAD and CVD.
3	Neuroendocrine factors - BDNF levels are found to be decreased during mood episodes. BDNF helps in maintaining the endothelial integrity as well. BDNF levels have been found to be reduced during acute coronary episodes while high serum BDNF levels are associated with decreased risk of CVD.
4	Autonomic dysfunction - Increased carotid intimal thickness has been found in BPAD which has been associated with higher systolic blood pressure.
5	Multisystem microvascular factors - Microvascular changes seen in cerebral, retinal, cardiac and peripheral blood vessels have been found to be risk factors for both BPAD and CVD, especially in younger population.
6	Hyperhomocysteinemia- Homocysteine levels have been found to be elevated in patients with BPAD and is a risk factor for development of CVD.
7	Genetic factors - Studies have found extensive genetic overlap between BPAD and CVD, with 129 shared loci though this needs further research.

Commonly found co-morbid psychiatric conditions in BPAD include substance use disorders, anxiety disorders, personality disorders, attention deficit hyperactivity disorders, conduct disorders

and eating disorders. The comorbid conditions often make the treatment challenging and the course and prognosis of the illness is also affected (45).

BPAD is a chronic relapsing illness and often the treatment is lifelong. Scales such as Young Mania Rating Scale(YMRS)(46), Bipolar Depression Rating Scale(BDRS)(47), Bipolar Affective Disorder Dimension Scale(BADDS)(48) can be used to supplement and document the illness.

Treatment of BPAD and cardiovascular disorders :

Pharmacological management is the mainstay of treatment (49,50). Baseline examination and investigations are a must and frequent monitoring is needed to assess if patients are at risk for CVD and other physical comorbidities. Common medications used include.

These guidelines recommend to optimize the management of bipolar mood disorders as detailed by Indian psychiatric clinical practice guidelines . ( )

The following guidelines are suggested to watch for the PHARMACOLOGICAL MANAGEMENT OF COMORBID issues of cardiovascular related side effects of the medications commonly used for mood disorders,. PL REFER to the guidelines suggested by indian psychiatry for clinical practice guidelines for mood disorders

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Following an acute episode MANAGEMENT , psychotherapies such as individual psychoeducation, CBT, IPSRT and family therapy have been found to be helpful in preventing relapses or worsening of mood episodes(51)Hence recommended.

TABLE 5: SHOWING THE PHARMACOLOGICAL AND CARDIOVASCULAR MANAGEMENT IN COMORBID PATIENTS

Class of medication	**Safety profile in CVD**
Mood stabilisers	Lithium - Causes weight gain. May cause sinus bradycardia, AV block, T wave changes, sinus node dysfunction**. Contraindicated** in sick sinus syndrome. Valproic acid - Associated with abnormal platelet function. But **no direct significant cardiac adverse effects.** Carbamazepine - Slows cardiac conduction and may cause high grade AV block. Should **be avoided** in patients with sick sinus syndrome and AV block. Oxcarbazepine - **No significant adverse effects.** Lamotrigine - **No significant side effects.**
Typical antipsychotics	Can cause prolonged QTc interval and predispose to TdP. Tachycardia and orthostatic hypotension are prominent side effects. Low potency antipsychotics (like chlorpromazine and thioridazine) cause more cardiac adverse effects when compared to high potency antipsychotics (like haloperidol) though risk is there with both. Thioridazine is cardiotoxic and is **to be avoided**.
Atypical antipsychotics	Clozapine, risperidone, quetiapine have been **more commonly associated with orthostatic hypotension.** Tachycardia is common, especially with clozapine. Ziprasidone, iloperidone, paliperidone have been associated with **prolonged QTc** interval **TO BE WATCHED.** **Metabolic side effects** such as obesity, hyperglycemia and dyslipidemia are more with clozapine, olanzapine, risperidone and quetiapine. Clozapine has been associated with myocarditis.**TO BE WATCHED** Atypical antipsychotics have been associated with sudden cardiac death. Aripiprazole is the antipsychotic with the safest cardiac profile.

Schizophrenia :

Patients with schizophrenia often have poor physical health due to various factors including sedentary lifestyle, poor nutrition, poor access to healthcare services, smoking etc. Their life expectancy is reduced when compared to the general population. Cardiovascular disease has been found to be the leading cause of death in this population. It is reported to be 2-3 times more in patients with psychosis when compared to control population. The predicted risk ratio of CVD in these patients is 1.3-1.64 though this might be underestimated. Myocardial infarction has been found in at least 30% of the patients with schizophrenia. CAD has been found to be around 27% in these patients while metabolic syndrome ranges from 36-52%. The prevalence rates of arrhythmias, acute coronary syndromes, hypertension, stroke and heart failure have been found to range from 1.43-2.17(52-54).

Mechanisms underlying the common link between schizophrenia and CVD include behavioural factors, effects of antipsychotics, biological factors such as inflammation, autonomic dysfunction, deficiency of long chain fatty acids, shared genetic loci between the two illnesses that have an effect on cholesterol levels, systolic blood pressure, and BMI(55,56).

Schizophrenia can be diagnosed using standard diagnostic criteria and course can be objectively documented using scales such as Positive and negative syndrome scale(PANSS)(57) and Brief psychiatric rating scale(BPRS)(58).

Mainstay of treatment is the use of antipsychotics. The efficacy and the safety profile of the same in CVD have already been discussed (SEE THE TABLE). Regular monitoring of the physical attributes such as weight, HTN, glucose levels, lipid levels, renal and liver function, and cardiac profile is absolutely needed in these patients. Psychological therapies also play a role in the prognosis of the illness.

Table 6: Suggested Cardiovascular considerations for prescribing psychotropic medicines.

1. Check for underlying cardiac illnesses like Ischemic heart diseases, acute coronary syndrome, uncontrolled hypertension,myocarditis, cardiomyopathy, heart failure etc.
2. Check for presence of congenital Long Qt syndrome.
3. Concurrent use of Digoxin or other medicines that can prolong QT interval.
4. Consumption of alcohol, nicotine dependence or dependence to any psychoactive substance.
5. Elderly, malnourished patients having multiple medical comorbidities.
6. Dose adjustments in patients having severe hepatic and renal impairments.

7. Special vigilance for patients having electrolyte imbalance, thyroid disorders, other chronic medical illnesses and terminal illnesses.
8. Proper training for CPR (Cardiopulmonary resuscitation) and availability of emergency medicines for resuscitation especially while using iv medications.

The life expectancy of persons with Schizophrenia and other severe mental disorders is reduced by 10 years due to adverse coronary outcomes than general population .

When cardiac medicines and psychotropic medicines are given together (like antihypertensives and psychotropic medicines), there is high chance of causing severe hypotension. Many psychotropic medicines alter the cardiac conduction with prolongation of PR, QRS and QTc intervals, ST segment depression, decrease T wave amplitude and large U waves in ECG. This effect is potentiated by synergistic effects of antiarrythmic drugs. SSRIs can displace other protein bound drugs and may lead to toxicity. Thioridazine. Chlorpromazine, Pimozide can prolong QT and QTc intervals (>450 msecs) and Pimozide can also lead to ultrastructural changes in cardiac muscles resulting in toxic cardiomyopathy. Clozapine can also cause cardiomyopathy and sudden cardiac death which is rare but TO BE KEPT IN MIND .

Anxiety disorders as comorbidity with cardiovascular disorders :

Anxiety disorders are common in patients with CVD and often affect the outcome of the cardiac illness. Many symptoms overlap between anxiety disorders and CVD such as chest pain, heaviness of chest, palpitations, dizziness, nausea, vomiting etc. This overlap of symptoms often makes diagnosis challenging.

Hence more often than not, patients with anxiety disorder present to emergency and get investigated for cardiac disorders(52,53). 20-30% of patients experience increased levels of anxiety following an acute coronary episode, the transient nature of which becomes chronic in at least half of the patients. Similar rates are seen in patients prior to CABG procedures. 13% of patients with heart failure have been found to have anxiety disorder while 20-40% of patients with implantable cardioverter defibrillator have elevated anxiety levels(52).

When the relationship between specific types of anxiety and CVD was assessed, it was found that patients suffering from GAD had a hazard ratio of 1.62 for CVD(54). Prevalence of GAD is 26% in patients with CAD and 14% in patients with HF. Prevalence of PTSD in CVD patients ranges from 6-24% while patients suffering from PTSD are found to develop CVD symptoms 20-65% more than controls(55). Prevalence of panic disorder varies from 5-8% in patients with CVD though some studies show higher prevalence. Anxiety, especially chronic illness, has been found to affect the mortality rate of patients in CVD, with poorer quality of life when compared to patients with CVD with no anxiety(56).

Biological mechanisms underlying anxiety disorder and CVD include autonomic dysfunction such as decreased heart rate variability, endothelial dysfunction, impaired HPA axis function and hypercortisolemia, inflammation, genetic factors such as pleiotropy etc.

Scales such as Hamilton Anxiety Rating Scale(HAM-A) (57)and Hospital Anxiety and Depression Scale(HADS) (58)can be used to assess the severity of anxiety symptoms(59).

Treatment OF ANXIETY DISORDERS AND CO EXISTING CARDIOVASCULAR DISORDERS:

SSRIs and SNRIs are the common class are commonly used to treat anxiety disorders. Benzodiazepines(BZDs) are often used for short term for symptomatic relief of anxiety symptoms. Studies have shown benzodiazepines to have beneficial effects in patients with CVD with no anxiety symptoms as well(60). Short acting BZDs like midazolam and triazolam, and intermediate acting BZDs like lorazepam and oxazepam are preferred over long acting preparations of BZDS to reduce drug drug interactions and additive effects of other CNS depressants used in CVD. No significant cardiac adverse effects have been found. Drugs like quetiapine and gabapentin can be considered second line medications as they have some efficacy in managing anxiety disorders.
Relaxation techniques, CBT, systemic desensitisation, flooding therapies and other appropiate behaviour and other psychotherapies and as important or psycho education and appropriate group therapies and family therapies are recommended. They are commonly used as psychological treatments for various forms of anxiety disorders. The evidence though exists is not robust but recommended.

Substance use disorders and cardiovascular disorders :

Non adherence to treatment is very common in patients who are suffering from mental illnesses. The emergence of metabolic syndrome characterized by obesity, diabetes, dyslipidemia, increased waist-hip ratio (WHR) and insulin resistance has put the persons with mental illness to added risk of suffering from cardiovascular disorders. **Less than 15% of patients having depression in coronary artery diseases (CAD) are actually being diagnosed**.(3,4,5)

Substance use disorders :

People with substance use disorders(SUD) are at a particular risk for both acute and chronic effects of the substances on the cardiovascular system(69). This group is very heterogeneous but few common risk factors are often seen. For example, injectable use might lead to thrombosis and embolism, infective endocarditis, sepsis, various transmittable illnesses such as HIV/AIDS and Hepatitis-B which also contribute to poor vascular health.

CVD is one of the leading causes of mortality in this group. We will be focusing on the most commonly used substances and their effects on cardiovascular system.

Alcohol:

Alcohol is one of the most common psychoactive substances used worldwide. There were few studies which reported that moderate levels of alcohol consumption is actually cardio-protective but overall consensus is that there are many harmful physical effects of alcohol though it is not so straight-forward. Alcohol has been shown to have an effect on lipoprotein levels, inflammation, endothelial function, and myocardium(70). Daily use of 1-2 standard drinks per day has been shown to either be protective or to not have a significant effect on the cardiac system. Higher use of alcohol, binge pattern of drinking, comorbid disorders, older age, and longer duration of use have been shown to increase the morbidity and mortality related to CVD(71).

Hypertension(HTN) is very prevalent among alcohol users and the relationship is dose-dependent on the amount of alcohol use. Incidence odds ratio of HTN in users of alcohol has been found to range from 1.2-2.3(72). HTN itself predisposes an individual to CAD, stroke and heart failure. According to a longitudinal cohort study in alcohol users, incident increased risk of myocardial infarction ranged from 1.4-1.5, that of atrial fibrillation was 2.08-2-19, and that of heart failure was 2.29-2.39(73). The relation between alcohol and peripheral vascular disease was found to be not very clear.

Nicotine:

Nicotine use especially in the form of smoking has been consistently linked with CVD since ages. Along with nicotine, other chemicals in the smoke have been found to be atherogenic, and carcinogenic, and also to increase the thrombogenic activity of platelets, increase cholesterol levels and insulin resistance. The carbon monoxide in the smoke also leads to supply demand mismatch of oxygen.

Nicotine has been found to cause dyslipidemia, HTN, and diabetes which are risk factors for CVD. Mortality due to CVD is 60 percent higher in those who use nicotine as compared to non-users(74). The INTERHEART study showed that smoking increased the risk of MI three-fold(75). Smoking is associated with a 60 percent increase in heart failure. There is a doubling of risk for arrhythmia in nicotine users. Nicotine use can be attributed as a cause of peripheral vascular disease by almost 50%. Risk of heart disease is almost 13% higher in users of smokeless tobacco when compared to non users. E-cigarettes also have negative health consequences, contrary to popular opinion.

Cannabis:

Cannabis is the most widely used illicit drug globally. It is known as the gateway drug and its use is more common in younger population. Endocannabinoid receptors in cardiovascular system may have a role in metabolism and vascular functioning. Cannabis consumption has been known to cause tachycardia, orthostatic hypotension, and dizziness.

Various case studies and reports have shown that cannabis can be linked to arrhythmias and sudden death. The annual risk of MI is found to be 1.5-3% in daily users of cannabis. Cannabis induced myocarditis may be a risk factor for development of peripheral vascular disease. Rarely, cardiomyopathy due to cannabis use has been reported. Overall, more studies are needed to know the chronic effects of cannabis on the cardiovascular system. Synthetic cannabinoids have also been found to cause tachycardia, acute changes in BP and probable MI(76).

Opioids:

Opioid use has slowly been increasing in the Indian subcontinent. It can include both prescription use and recreational use. Infective endocarditis has been consistently linked to use of injectable opioids. However, other cardiac adverse effects have been studied less frequently. Opioid receptors have been discovered in the cardiac system but the biological link between opioids and CVD has been poorly understood. There are studies that report the cardioprotective effects of opioid use while other studies talk about the harmful effects. Opioids have been used in cardiac patients and for cardiovascular thoracic surgeries. Only more research in this area

shed a light on the relation between opioid use and CVD(77,78).

Opioids such as tramadol and methadone have been associated with prolonged QT interval and can predispose to arrhythmias and TdP(Torsade de Pointes)(79). Risk ratio of CAD in opioid use ranges greatly from 0.5-3.09 (80). It is possible that lifestyle factors and co-morbid substance use might play a contributory role.

Treatment :

Treatment includes symptomatic management of withdrawal symptoms and use of agents to prevent craving and relapse(81-85).

Table 7: Cardiac Safety of Pharmacotherapy of Alcohol and Substance use

Disorder	Safety profile of medications used
Alcohol use disorder	Acamprosate - **No significant** cardiac side-effects. Clonidine - Might cause severe hypotension, syncope, bradycardia, AV block, rarely CHF. **To be used with caution**. Disulfiram - Adverse effects include tachycardia, dizziness, hypotension, rarely MI and CHF. **Not recommended** in CVD. Naltrexone - No significant cardiac side effects. BZDs - **No significant** adverse effects
Nicotine use disorder	Bupropion - **No significant** adverse effects Varenicline - Small risk of CAD and PVD.

	Nicotine replacement therapy - Might cause tachycardia, dizziness, elevated BP.

Opioid use disorder	Methadone - Prolonged QT interval, TdP, pathological U waves, cardiomyopathy, CAD, Brugada-like syndrome. **Not recommended**. Buprenorphine - Might cause orthostatic hypotension, syncope and arrhythmias. **To be used with caution.** Tramadol - Might cause arrhythmia, prolonged QT interval, tachycardia. **To be used with caution.** Clonidine - Might cause severe hypotension, syncope, bradycardia, AV block, rarely CHF. To be used with caution. Naltrexone - **No significant cardiac side effects.** BZDs - **No significant adverse effects**

Psychological therapies include psychoeducation, motivational interviewing, motivational enhancement therapy, CBT, relapse prevention strategies, and family therapies. SUD is a chronic and relapsing disorder, hence long term management is needed(86).

Table 8 : Safety of drugs in specific illness(87-95) :

S no	Cardiovascular disorder	Drugs preferred
1	**Hypertension**	**Antidepressants : SSRIs, Reboxetine, Mirtazapine, Agomelatine** **Antipsychotics : Quetiapine, Risperidone, Olanzapine, Paliperidone, Iloperidone** **Others : Valproic acid, Benzodiazepines, Methadone, Donepezil, Rivastigmine**
2	**Coronary Artery Disease**	**Antidepressants :**

		Sertraline, Escitalopram, Fluoxetine, Mirtazapine, Vortioxetine, Agomelatine, Bupropion, Buspirone **Antipsychotics :** **Aripiprazole, Olanzapine, Lurasidone** **Others :** **Valproic acid, Topiramate, Benzodiazepines, Donepezil, Rivastigmine, Buprenorphine**
3	**Congestive Heart Failure**	**Antidepressants : All SSRIs except Citalopram, Mirtazapine, Bupropion, Agomelatine** **Antipsychotics :** **Aripiprazole, Lurasidone, Olanzapine** **Others : Valproic acid, Benzodiazepines, Donepezil, Methadone, Buprenorphine**
4	**Arrhythmias(Ventricular tachycardia, Torsades de Pointes, Prolonged QT interval etc.)**	**Antidepressants :** **Sertraline, Fluoxetine, Paroxetine, Mirtazapine, Bupropion** **Antipsychotics :** **Aripiprazole, Lurasidone** **Others :** **Valproic acid, Benzodiazepines, Buprenorphine**
5	**Valvular heart disease**	**Antidepressants :** **SSRIs except Citalopram, Mirtazapine** **Antipsychotics :** **Aripiprazole** **Others :** **Benzodiazepines, Buprenorphine**

Electroconvulsive therapy(ECT):

Electroconvulsive therapy or ECT is one of the most effective treatments in psychiatric practice. Though there are no absolute contraindications for ECT, one of the relative contraindications include recent unstable angina or MI(within 30 days). ECT and the drugs used in it cause both sympathetic and parasympathetic changes leading to changes in cardiac output, blood pressure, and heart rate. Complications include arrhythmias, ischemic changes, and heart failure. In patients with pre-existing cardiac conditions, these changes may compromise the cardiovascular health in them(96). Hence, utmost caution is needed when ECT is given in them.

Following steps are recommended.

1. High risk consent should be taken from the patients and their relatives for ECT procedure.
2. Pre-anaesthetic evaluation and pre-ECT cardiac evaluation are needed to assess for fitness of the patient.
3. If seizure duration is more than a minute,then seizure should be aborted to reduce the stress on the myocardium.
4. Oxygen supplementation should be provided continuously.
5. Post ECT, monitoring should continue in the post-anesthesia care unit or a high dependency unit.

Management of psychiatric patients developing new onset cardiovascular illness:

It is well known that psychiatric patients, whether secondary to illness, psychotropic use or psychosocial factors, have an increased risk for development of cardiovascular disease. Regular screening for physical illnesses is needed. However, majority of the patients do not have proper evaluation due to various factors. If and when they develop CVD, the following steps are recommended.

In case of chronic cardiovascular conditions, the cardiologist/ primary care physician should consult with the psychiatrist and decide on pharmacological management taking into account the past and present symptomatology of the psychiatric condition, severity of the illness, need to continue the psychotropic and select an efficacious drug which also has a good safety profile in cardiac patients with minimal interactions with the cardiac drugs.

In case of acute cardiac illnesses such as MI or cardiac surgery, psychiatrist should be consulted in an emergency basis regarding the cessation of the drug till the acute illness is treated. The drug should be restarted at the earliest as post MI or cardiac surgery, exacerbation of previous psychiatric illness is often seen. Drugs which have a better safety profile and least drug drug interactions should be preferred with regular follow up.

How to manage in the case of prolonged QT interval :

When should we intervene?

If QTc interval is less than 440ms(men) or 470ms(women) - no need to intervene
If QTc interval is more than 440ms(men) or 470ms(women) but less than 500ms -

1. Repeat ECG
2. Consider reducing the dose of the drug
3. Consider switching to a low risk drug
4. Consider a cardiology review
5. Review other causes of prolonged QTc interval

If QTc interval is more than 500ms -

1. Stop the suspected causative drug
2. Switch to a low risk drug
3. Review with a cardiologist at the earliest
4. ECG monitoring if patient is showing symptoms such as syncope
5. Review other causes of prolonged QTc interval

Table 9(97)

Drugs with low risk of causing QTc prolongation	Aripiprazole Olanzapine Perphenazine Lurasidone Sertraline Desvenlafaxine Bupropion Vilazodone Reboxetine Mirtazapine Valproic acid Topiramate Carbamazepine Oxcarbazepine Lamotrigine Gabapentin Pregabalin Benzodiazepines Trihexyphenidyl and Biperiden Buprenorphine
Drugs with moderate risk of causing QTc prolongation	Amisulpride Clozapine Quetiapine Risperidone Paliperidone Flupentixol Citalopram Escitalopram

	Fluoxetine Paroxetine Venlafaxine Duloxetine Amitriptyline Nortriptyline Clomipramine Imipramine Doxepin Moclobemide Lithium Methadone
Drugs with high risk of causing QTc prolongation	Chlorpromazine Haloperidol Pimozide Sertindole Ziprasidone

Special populations :

Children -

Pre-existing cardiac disease in children increases their susceptibility to adverse cardiac side effects due to use of psychotropics, in particular QT prolongation and arrhythmias(98). Caution is needed when prescribing drugs in these children. Baseline ECG and investigations including extensive physical examination should be done before initiating therapy in them. Careful monitoring of any adverse effects should be done as long as the child is on these medications.

In case of using stimulants such as methylphenidate in children with ADHD, studies have shown an increased relative risk of arrhythmias and myocardial infarction though absolute risk is low(99). Monitoring should be done rigorously especially in the early stages of the treatment as risk is high during these periods. The psychiatrist should be in regular and frequent communication with the paediatrician/cardiologist to minimise risks.

Geriatric population-

Physical comorbidities are the rule rather than the exception in this population, often multiple in nature. Illnesses, prescription of multiple drugs, and the drug drug interactions often lead to significant adverse effects in the elderly.

Before starting any psychotropic, complete history of all the physical conditions, careful review of the medications currently in use and extensive physical examination are needed. Drugs with minimal drug interactions should be started at low doses. Oral treatment is preferable to parenteral treatment as rapid introduction of the drug may cause serious side effects. Use of antipsychotics

has been shown to cause sudden deaths in patients, especially in those with dementia. Hence, extreme caution needs to be applied.
Anticholinesterases are often used frequently in this population. It has been shown that the regularly used drugs of this class such as donepezil, rivastigmine, and rivastigmine do not have any significant adverse cardiac effects in the patients and hence can be used safely(100).

In summary:

The guideline suggested is based upon the best evidence available at this point of time. As in the clinical practice guidelines of Indian psychiatry it is important to individualize and evaluate the cardiovascular issues in each case of psychiatric illness. Also it is important to do a regular work up basically with electrocardiogram in day to practice.
Needed blood chemistry, and in liaison with cardiologist work up for the cardiovascular work up. The suggested guidelines as detailed in this chapter have to be personalized to every psychiatrically ill patient . These guidelines further emphasize the need to take care of both cardiovascular disorders and psychiatrically patients need to be taken care simultaneously.

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Management of psychiatric disorders in patients with respiratory diseases.

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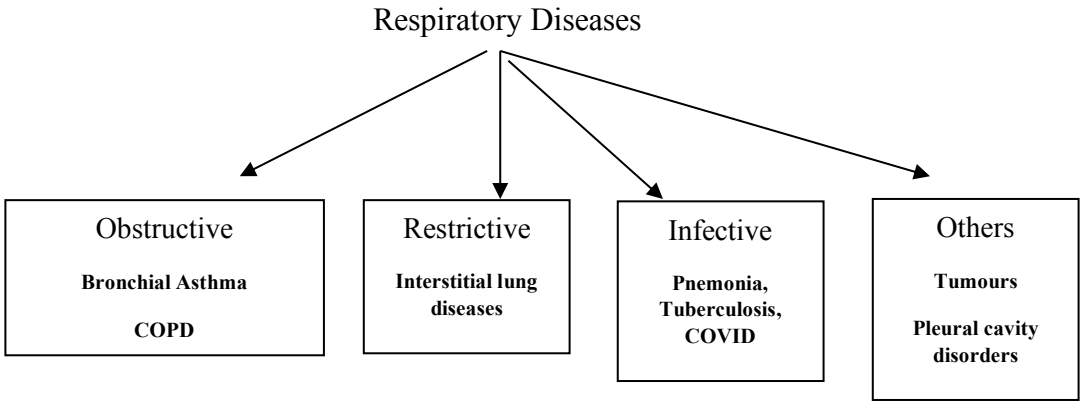
Abstract: The management of medical illnesses with psychiatric disorders and vice versa are ever challenging with the rise of comorbidities and 'dual diagnoses'. The situation has become more challenging especially in the light of COVID pandemic. The management of psychiatric disorders in patients with respiratory diseases is very challenging. It requires knowledge, skill and expertise following some ground rules. These recommendations may be adopted in general and considered in the light of individual merit.

Introduction: The respiratory diseases can be broadly classified into obstructive, restrictive, infective and other groups as shown in figure 1 which will be addressed in this guideline. This chapter will also incorporate the respiratory adverse effects of various psychotropic drugs with special mentions about smoking cessation, obstructive sleep apnoea (OSA) and management of COVID related respiratory diseases.[1]

Figure 1: Classification of respiratory diseases



The various considerations of managing psychiatric disorders in patients of respiratory diseases can be summarized in broad headings e.g in acute or critical care settings, substance use disorders with respiratory diseases, chronic care settings, psychiatric disorders in chronic respiratory diseases, COVID and psychiatry especially the neuropsychiatric manifestations of COVID, management of Obstructive Sleep Apnoea (OSA) with psychiatric comorbidities, management of psychogenic dyspnoea (hyperventilation syndrome) and pharmacological adverse effects of psychotropic medicines.

ACUTE CARE SETTING

The management of psychiatric comorbidities of respiratory diseases in acute settings is very challenging in the purview of sedative infusions, choosing the appropriate psychotropic medicines, drug-drug interactions etc have been summarized in Table 1.[2] Detail management of psychiatric disorders in intensive care unit will be dealt in a separate chapter.

Table 1 summarizes the role of different psychotropic medicines in acute care settings.

Table 1: Salient points on use of psychotropics in patients with lung disease in critical care settings.

Sedative agents:	
Dexmedetomidine (selective alpha2-receptor agonist)	favourable risk-benefit profile minimal delirium inducing property.
Standard sedatives (propofol, benzodiazepines, opioids)	may cause respiratory depression/ worsen delirium. Increased risk of nosocomial infection.
Antipsychotics	
Quetiapine	More sedating, shorter half-life (6 hours)
Olanzapine	More sedating, longer half-life (30 hours) Both having high anticholinergic property. Caution needed during discontinuation, as may worsen bronchoconstriction.
Haloperidol	Intermediate half-life (20 hours), minimal anticholinergic property.
Aripiprazole, Risperidone	Less sedative. Preferred for hypoactive delirium.
Aripiprazole, Lurasidone	Minimal effect on QTc.
Antidepressants	
Paroxetine	Short half-life; caution for cholinergic rebound. May worsen pulmonary hypertension.
Venlafaxine	Short half-life. Sudden withdrawal may cause serotonin withdrawal.
Mirtazapine	Chance of CO2 retention.
Buspirone	Improves exercise tolerance and dyspnoea.
Drug–Drug Interactions ❖ SSRIs, tobacco smoking- Enzyme induction CYP1A2, 2B6, and 2D6. ❖ Rifampicin- cytochrome P450 3A4 substrate and might compete with many psychotropics. ❖ Linezolid and Isoniazid- weak monoamine oxidase inhibitors; caution needed to be	

used with MAOIs, SSRIs, SNRIs. ❖ Theophylline- decrease levels of lithium by up to 20% to 30%.
Cystic Fibrosis ➢ GI absorption of psychotropics are typically slow d/t ion transport abnormality. ➢ Lumacaftor/ ivacaftor (gene-modulating medications) decreases the levels of SSRIs and antipsychotics via CYP interactions. ➢ SSRIs to be used with caution d/t hepatic dysfunction and decreased platelets associated with CF resulting in risk of bleeding.

The pulmonary medicines causing neuropsychiatric side effects are a matter of concern.[3] The common group of drugs that is responsible for these adverse effects are summarized in Table 2.

Table 2: Neuropsychiatric side effects of pulmonary medications

Medications	**Neuropsychiatric Side Effects**
Steroids	Restlessness, anxiety, insomnia, cognitive dysfunction, delirium, manic symptoms, psychosis. Depression (long-term use and while tapering off)
Beta2-agonists Albuterol Levalbuterol Salmeterol	Anxiety, tremor, insomnia
Mixed alpha-agonists and beta-agonists Epinephrine Ephedrine Phenylephrine Phenylpropanolamine	Anxiety, tremor, insomnia, psychosis
Methylxanthines Theophylline	Insomnia, jitteriness, anxiety, irritability, panic
Anticholinergics Atropine	Hallucinations, paranoia, memory loss, delirium, agitation
Leukotriene inhibitors Montelukast	Dizziness, fatigue, asthenia, suicidal ideation
Acetazolamide	Confusion and malaise

Calcineurin inhibitors (in transplant patients) Tacrolimus Cellcept Sirolimus	 Anxiety, tremor, anxiety, psychosis, delirium, PRES
Antimicrobials: Cephalosporins (cefepime, ceftazidime) Antimycobacterial (isoniazid) Penicillin Sulfonamides Metronidazole Macrolides (clarithromycin) Quinolones (ciprofloxacin)	 Delirium, psychosis Delirium, seizures, myoclonus Psychosis Delirium, cerebellar signs

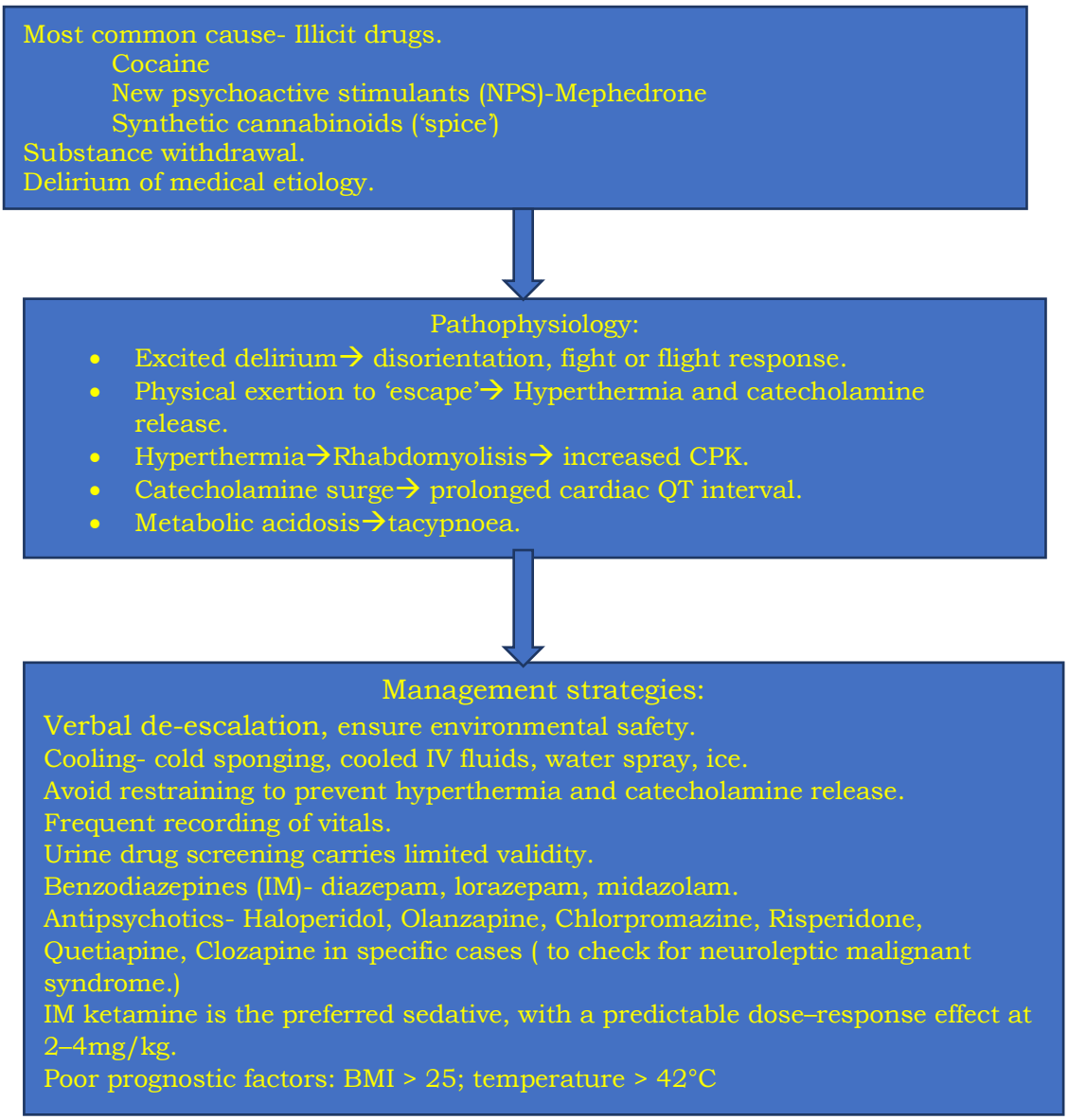
The management of delirium is always very challenging, it requires finding out the underlying cause. The challenge after diagnosing of hypo or hyperactive delirium demands proper selection and appropriate strategies which have been summarized in Table 3. Timely diagnosis of psychiatric or behavioural side effects arising from systemic drugs is an indispensable aspect to avoid significant number of morbidities or mortalities. Medication-related factors like polypharmacy, use of higher dosing, faster administration, parenteral route, and patient related factors like presence of premorbid mental illnesses, hepatic or renal insufficiency, augmented permeability of the blood-brain barrier (e.g., meningitis or porphyria), very young or elderly patients are the major risk factors to develop such side effects. The common scenario in acute care settings is delirium where a psychiatrist is frequently called for. In respiratory care settings careful assessment of the respiratory system medications, history of recent substance abuse/ intoxication or withdrawal, finding the actual medical cause of the acute behavioural disturbance (ABD) state, choosing appropriate medication to manage the situation are the critical tasks for a psychiatrist. The general principles[2] to use psychotropics in acute care, culprit respiratory drugs for developing psychiatric side effects are summarised herewith.[4]

Table 3: General Principles for psychotropics used in delirium.
One drug at a time
Use of sedatives and antipsychotics to be kept minimum
Titrate for optimum, not maximum; Discontinue as clinical picture improves.
Doses need to be tailored according to age, weight and most importantly degree of

agitation
Small frequent doses are preferred over longer and larger doses.
Review at least every 24 hours
If 'SOS' or 'as needed' doses are required frequently, scheduled doses should be optimised accordingly.
Clear plan of weaning to be documented if discontinuation is not possible in acute care settings.

The Flowchart1 describes the pathophysiology and management strategies.

Flowchart 1: Drug-induced acute behavioural disturbance (ABD) in acute Admissions



SUBSTANCE USE DISORDER AND PULMONARY DISEASES

Managing 'dual diagnosis' (major psychiatric disorder along with substance use disorder) is challenging. It becomes more challenging with the presence of 'triple diagnosis i.e along with this the presence of medical comorbidities. Illicit drug use constitutes a major health problem and associated with diversified thoracic complications. In case of dependent pattern of use, respiratory system's inherent ability to recover from toxic exposure or substance-mediated injury may become overwhelmed, resulting in chronic pulmonary diseases. Tobacco smoking-related respiratory damage is often slow and progressive. Cigarettes/ bidi contain hundreds of toxic compounds including carcinogens. Quitting smoking at any time, at any stage of life or disease is beneficial. The proper tobacco cessation program must have to be planned accordingly. Although cannabis is less associated with cancers, however bronchitis, emphysema, increased risk of respiratory infections is not uncommon. As a stimulant drug, cocaine is associated pulmonary hypertension, blood vessel constriction, and ischemic heart tissue damage. Smoking cocaine is associated with "crack-lung" (triad of haemorrhages, pulmonary oedema, fluid retention in the lungs) along with increased risk of cancer. Chronic opioid users may be at risk of hypoxia, exacerbation of obstructive sleep apnoea, bronchitis, and emphysema, decreased immunity or pulmonary oedema. Inhalant abuse may be associated with acute lung injury, or even increased propensity to thrombo-embolic disease.[6] The potential severity of causing lung diseases of various psychoactive substances has been described in Table 4. The details of management of such issues are discussed in clinical practice guideline for substance use disorders of Indian Psychiatric Society.

Table 4: Substance Use Disorders and Pulmonary Diseases.

Substance	Associated pulmonary disease
Tobacco	Risk factor for the development of COPD and lung cancer, detrimental to any pulmonary condition.
Cannabis	Lung cancer Respiratory symptoms suggestive of obstructive lung disease. Allergic bronchopulmonary fungal disease, with species of Aspergillus, Mucor, Penicillium, and thermophilic actinomycetes having all been cultured from samples of marijuana.
Opioids	Suppress the respiratory drive. Associated with deaths due to respiratory failure. Aspiration pneumonia, acute respiratory distress syndrome (ARDS) and sepsis. Opioid overdose is a common reason for ICU admission-oxycodone and hydrocodone and the most commonly co-ingested substances are benzodiazepines, followed by methamphetamines. Increased association with treatment resistant tuberculosis
Alcohol	Increase susceptibility to respiratory infections and lung injury. Increased risk of developing ARDS.

Methamphetamine and cocaine.	Idiopathic pulmonary arterial hypertension/ PAH Crack lung, an acute pulmonary syndrome occurring up to 48 hours after cocaine inhalation, characterized by radiologic evidence of alveolitis and histologic findings of diffuse alveolar damage and hyaline membranes. Spontaneous pneumothorax, pneumomediastinum, bronchitis, pneumonitis, and bronchospasm (when smoked)
Inhalant Nitrous oxide	Increased level of methyl malonyl-CoA and homocysteine. Elevated homocysteine is a risk factor for venous thromboembolic disease, which can lead to pulmonary embolism and present as a medical emergency.

CHRONIC CARE SETTING

Psychiatric disorders in chronic respiratory diseases

Chronic respiratory diseases or CRD are long term diseases involving the airway and other structures of the lung. Among the CRDs, Chronic Obstructive Pulmonary Disease [COPD], Asthma, Occupational Lung Diseases, Pulmonary Hypertension are the most common. It has been seen that a major percentage of patient with COPD suffers from psychiatric issues, depression and anxiety being most common. Additionally, prevalence of depression and anxiety is almost 6 times more in asthma patients than in general population. We will discuss about the management of psychiatric disorder in COPD and asthma here.

Chronic obstructive pulmonary diseases

Global Initiative for Chronic Obstructive Lung Disease [COLD] has termed COPD as a disease which is characterised by limitation of airflow, partially reversible presenting as breathlessness and other relevant systemic findings. In contrast to asthma, the limitation of airflow in COPD is almost irreversible and usually it worsens as time proceeds. One of the main causes attributed to COPD is smoking, which is well prevalent in patients with psychiatric disorders.

COPD is one of the leading causes of mortality and morbidity worldwide. Studies show that anxiety and depression is very much co-morbid with COPD in both young and old patients. The spectrum of co-morbidity ranges from significant symptoms to full diagnosis of mental disorders as per DSM or ICD. It has been seen that anxiety in COPD patients is often co-morbid with depression and also depressed patients with COPD presents with overt anxiety symptoms. The common symptoms of depression and anxiety in COPD are as follows:

1. Fatigue
2. Weight changes
3. Sleep Disturbances
4. Agitation
5. Irritability
6. Difficulty in concentration

Other studies demonstrate high prevalence of cognitive dysfunction in patients with COPD. The cognitive dysfunction specifically presents with deficits in verbal skills, verbal memory but preserved verbal attention. The classification of cognitive, mood and anxiety disorders in patients suffering from COPD has been summarized in Table 5.[7]

Table 5: Classification of disorders of cognitive, mood and anxiety in patients suffering from COPD.

Cognitive disorders	Mood disorders	Anxiety disorders
1. Delirium 2. Dementia 3. Amnesia 4. Mild cognitive impairment	1. Major depressive disorder. 2. Bipolar disorder. 3. Dysthymia	1. Generalized anxiety disorders. 2. Panic disorder. 3. Social anxiety disorder. 4. Post traumatic stress disorder. 5. Specific phobia

Treatment of cognitive disorders in COPD

Improved cognition in COPD patients have shown to decrease the disease outcome like acute exacerbations, hospitalisation rate and improve quality of life. Oxygen therapy is found to be efficacious in case of cognitive disorders in COPD as it improves the cerebral blood flow. Researchers have found that continuous oxygen therapy was better than Nocturnal oxygen therapy trial [NOTT] in reducing mortality rate.

Pulmonary rehabilitation has been processed for chronic respiratory impairments. It improves the cognitive function since diminished aerobic fitness is a risk factor for cognitive decline. It is an individualised programme delivered to the patient and the family by the therapist. Details are discussed afterwards.

Regarding pharmacological therapy, limited data exists. Formoterol, a beta 2 agonist used to treat COPD has shown some efficacy in improving synaptic density and cognitive function. Roflumilast, a PDE-4 inhibitor has also shown some improvement in cognitive functions in COPD patients. For patients with delirium, low dose haloperidol or any other second-generation antipsychotics can be used depending on the patient profile. Management of co-morbid psychiatric issues are necessary. Role of cognitive enhancers are doubtful. The assessment (Flowchart 2) management of mild and moderate (Table 6) and severe cognitive dysfunction (Flowchart 3) have been summarized below.[8]

Flowchart 2: Assessment of cognitive dysfunctions in COPD

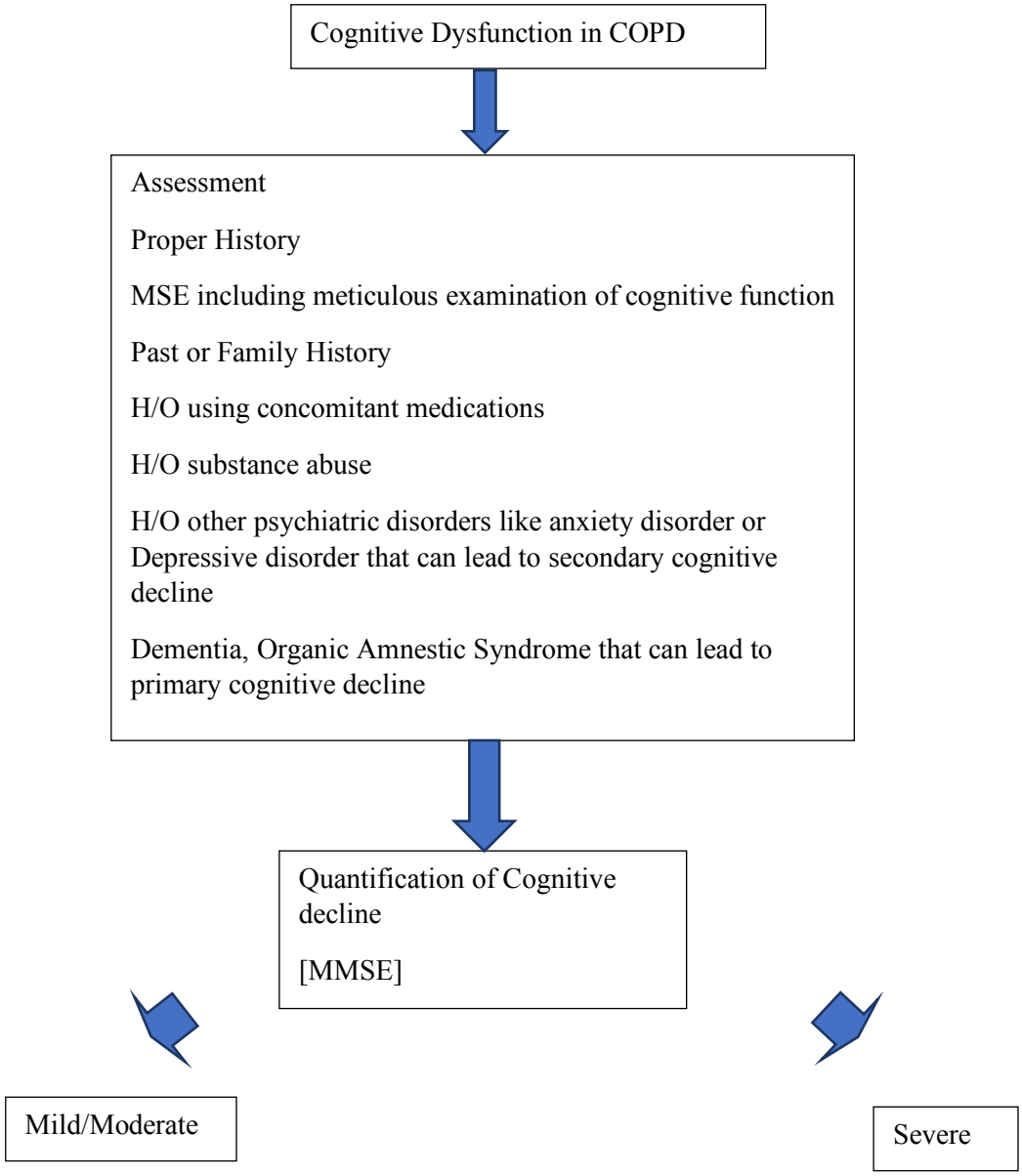


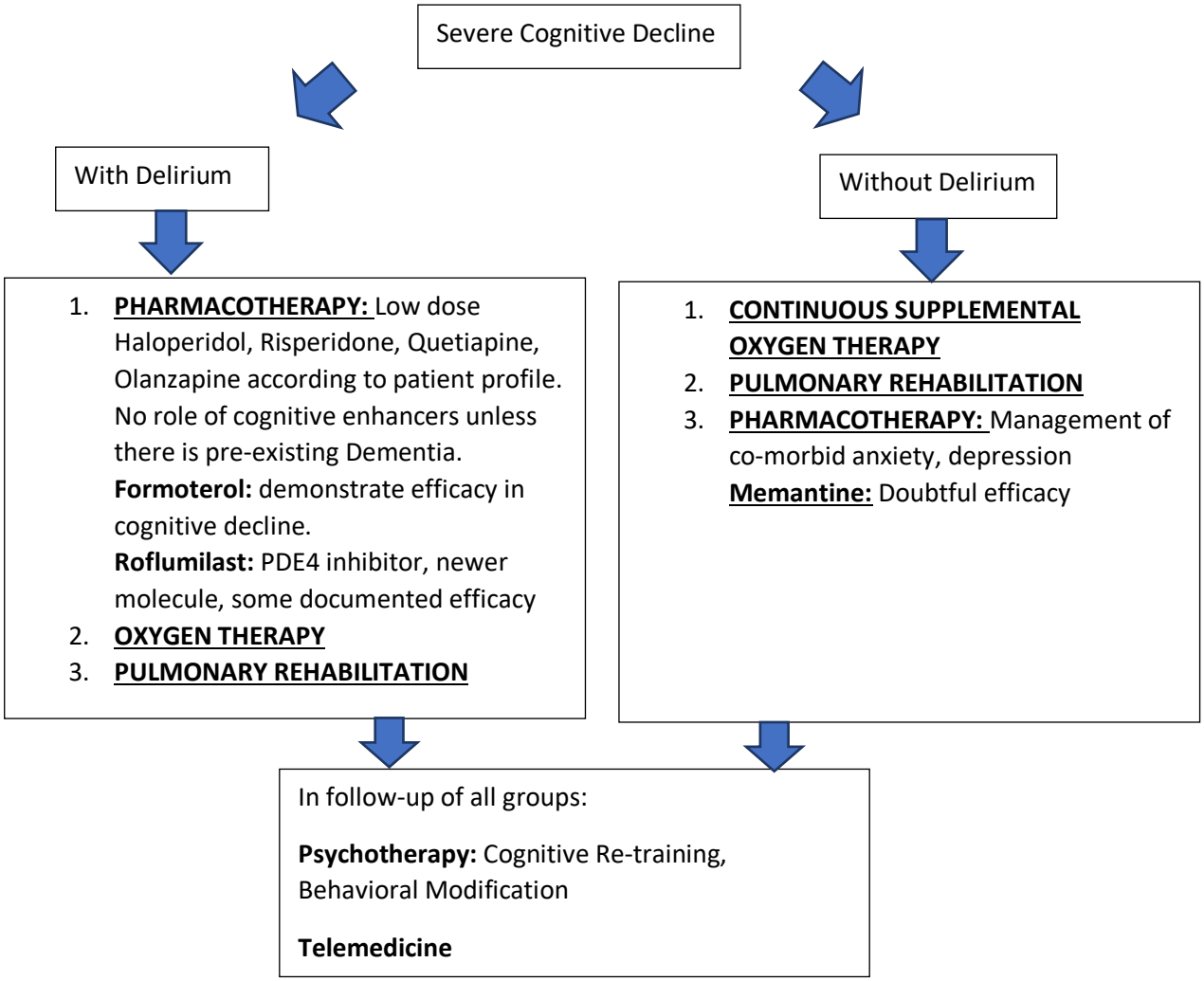
Table 6: Treatment of Mild/Moderate cognitive disorders in patients suffering from COPD.

1. **OXYGEN THERAPY:** Continuous oxygen therapy is better than nocturnal oxygen therapy. It improves cognitive function in long term, slows cognitive decline, decreases mortality. It also improves cerebral blood flow.

2. **PULMONARY REHABILITATION:** Improves exercise capacity, improves cognition.

3. **PHARMACOTHERAPY:** Mostly used in secondary psychiatric issues. Sedatives, if used, should be of less duration to slow cognitive impairment. No definite role of cognitive enhancer.

Flowchart 3: Treatment of severe cognitive decline in patients suffering from COPD.



Pulmonary rehabilitation

Pulmonary rehabilitation, also known as Respiratory rehabilitation, is an important part of COPD management among patients, who continue to remain symptomatic despite standard medical treatment. The aim of the rehabilitation is to improve the well-being and quality of life of the patient and the caregiver. The main component of the rehabilitation is the supervised pulmonary exercises, which helps in addressing the issues like ventilatory limitation, gas exchange limitation, cardiac dysfunction, skeletal muscle dysfunction, respiratory muscle dysfunctions. The other components include smoking cessation, emotional support and nutritional support to improve the general quality of life of the patient.[9] The indications and components of pulmonary rehabilitations have been summarized in Table 7A and 7B.

Table 7A: Indications of pulmonary rehabilitation.

1. OBSTRUCTIVE DISORDERS
    - Chronic Obstructive Pulmonary Disorder
    - Persistent Asthma
    - Bronchiectasis
2. RESTRICTIVE DISORDERS
    - Interstitial Fibrosis
    - Sarcoidosis
    - Kyphoscoliosis
    - Parkinson's Disease
    - Lung Cancer
    - Pulmonary Hypertension
    - After Lung Transplant
    - Before and after Lung Surgery

Table 7B: Components of pulmonary rehabilitation.

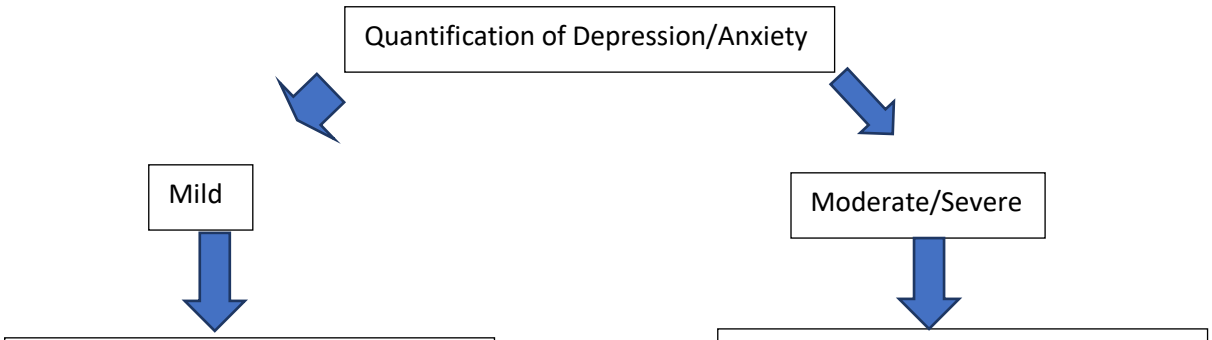
1. Exercise training
2. Inspiratory muscle training
3. Neuromuscular electrical stimulation
4. Facilitate smoking cessation
5. Optimize pharmacotherapy
6. Detect and manage acute exacerbations
7. Manage acute dyspnea
8. Increase physical activity
9. Nutritional evaluation
10. Promote mental health
11. Advanced care planning

Treatment of anxiety & depressive disorders with COPD

Treatment of anxiety and depressive disorders in patients suffering from COPD involves both pharmacotherapy and psychotherapy. For mild to moderate depressive disorder, the first line of treatment is psychotherapy. Several modes of psychotherapy can be done depending on the patient's needs. Cognitive behavioural therapy, group psychotherapy, interpersonal therapies are the few options. For moderate to severe depressive or anxiety disorders, pharmacotherapy is the first line of drug.

SSRIs are the first choice as antidepressants. Alternatively, SNRIs can be used. Drugs should be used judiciously and half-life, drug-drug interactions should be kept in mind. Precautions should be taken while using fluoxetine, as it has a longer half-life. Fluoxetine, fluvoxamine, and paroxetine are CYP3A4 inhibitors, should be used cautiously with COPD drugs. TCA s should better be avoided, as anticholinergic side effects are more prominent in elderly persons, can cause sedation too. NDRI/NaSSA can be used as 2nd line of drug. Benzodiazepines should be used in low dose and for minimum duration. Augmentation can be done with second generation antipsychotics or mood stabilisers depending on the patient profile. Lithium should be used very cautiously as COPD patients are already prone to dyselectrolytemias.[10] Other treatment options in addition to pharmacotherapy involve psychotherapy and pulmonary rehabilitation. Management approach has been described in Flowchart 4.

Flowchart 4: Management of depression and anxiety disorders in COPD



1. **Psychotherapy** is the initial treatment of choice:
   - CBT
   - Group Psychotherapy
   - Relaxation Therapy
   - Mindfulness based intervention [MBI]
   - Deep Breathing Exercise
   - Yoga Therapy
   - Music Therapy
2. **Pharmacotherapy:** Indicated only when inadequate response to psychotherapy.

SSRI/SNRI is the first choice

3. **Pulmonary Rehabilitation**

1. **Pharmacotherapy:**Treatment of choice, should be judiciously used [short half-life, less drug interaction, less interaction with pulmonary pathology, less sedation]. Start with low dose, go slow.
   SSRI/SNRI: 1st choice of drug [**Fluoxetine, Fluvoxamine, Paroxetine**should be avoided, as they are CYP3A4 inhibitor, can cause drug interaction. Fluoxetine also has long half-life.]

   NDRI/NaSSA/TCA:2nd line Careful about TCA, as they can cause cardiac complications and sedation.

   Augmentation:
   Second generation anti-psychotics: optimum balance of risk-benefit ratio to be maintained.
   Mood Stabilizers: careful about Lithium, as they can cause dyselectrolytemia in COPD patients.

2. **Psychotherapy:** Same as before.

3. **Pulmonary Rehabilitation**

Bronchial asthma.

Asthma is a common chronic respiratory disorder that involves inflammation of airway. During acute exacerbations, the patient complains shortness of breath, chest tightness, coughing and wheezing. Asthma can usually be managed with rescue inhalers to treat symptoms (salbutamol) and controller inhalers that prevent symptoms (steroids). Severe cases may require longer-acting inhalers that keep the airways open (formoterol, salmeterol, tiotropium), as well as inhalant steroids.

Similar as COPD, epidemiological studies have shown that asthma is associated with elevated risk of psychiatric conditions including anxiety disorders, depressive disorders, alcohol use disorder, schizophrenia and suicide. During acute exacerbations, patients with asthma faces anxiety, panic, irritability, frustrations closely resembling psychiatric symptomatology. The experience of the respiratory disease may lead to secondary psychiatric problem. Similarly, psychopathology may result not alteration of immunological/ inflammatory pathway involved in asthma. Thus, asthma symptoms present in childhood often presents with anxiety disorder in adulthood. Elevated levels of a range of psychiatric conditions are found in the first-degree relatives of asthma patients. This also explains the genetic basis.

Existing psychiatric disorder and asthma can influence each other in various ways. Overlap of symptoms can cause challenges in the diagnosis and treatment of both asthma and psychiatric disorders. Prominent positive symptoms of schizophrenia can distract physicians from co-morbid asthma and lead to underdiagnosis and undertreatment. Similarly, patients with panic disorder with co-morbid asthma seem to have higher rates of hospitalisation and emergency room visit due to “panic-fear”. Strong emotional states associated with psychopathology may affect asthma directly mainly through parasympathetic excitation, hyperpnea and hypocapnia. Psychiatric patients with altered mood can also affect disease management of asthma, for examples: over or underuse of rescue inhalers, lack of adherence to treatment protocols, neglect of trigger control, problem behaviour like smoking, delayed treatment seeking etc. symptoms of asthma can be an origin to panic and lead to fatigue and exhaustion experienced in psychiatric disorders. Internalizing disorders in children seeking cognitive behaviour treatment are more serious in those co-morbid with asthma.[11]

Asthma is also associated with an increased risk of cognitive disorders like mild cognitive impairment, and diagnosis of asthma in early life increases the chance of development of dementia in later life. The association between asthma and cognitive disorders are not known, but could be related to reduction in respiratory functions, inflammatory processes. Medication treatment for both asthma and psychiatric disorders has adverse effect. High doses of benzodiazepines and hypnotics can lead to respiratory depression. SSRI s are the first line of choice for depression and anxiety. For treatment guideline, same can be followed as in COPD.

Adjunctive Cognitive and Behavioural Treatment Modalities for Asthma

These are treatment modalities that have been adapted for asthma, not directed towards treating co-morbid psychiatric conditions but to reach the psychologically relevant deficits in patients with asthma, such as maladaptive breathing patterns, inaccurate perception of airway obstruction, or suffering from excessive stress.[12]

1. **Training of breathing pattern:** Certain breathing patterns can hyperpnea or hypocapnia and increase asthma symptoms. These are replaced by more slow, abdominal, shallow, more regular and or nasal breathing by training modalities. This can induce a better gas exchange efficiency. Feedback can also be provided to increase respiratory sinus arrhythmia, which has been associated with similar benefits.
2. **Interoception training:** This can address a potentially dangerous lack of awareness of airway obstruction in patients with asthma. It is often administered to make the patient understand the different loads or to lower their perceptual thresholds for just noticeable load.
3. **Others:** Various forms of yoga, meditation, relaxation exercises are administered to decrease the distress associated with asthma.

LUNG CANCER

Lung cancer accounts for twenty percent of all cancer deaths worldwide. Tobacco is the primary risk factor for lung cancer, others being passive smoking, exposure to asbestos, radon and other carcinogenic agents. The major reason for poor survival of lung cancer is lack of early detection and treatment measures. The most common histological type of lung cancer is non-small cell lung carcinoma [NSCLC] followed by small cell lung carcinoma [SCLC].

Table 8A: Risk factors for depression in lung cancer patients.

1. Old age
2. Advanced disease stage
3. Secondary to organ failure or from nutritional, endocrine, neurological complications of cancer.
4. Presence of other co-morbid medical illness
5. Previous h/o depression
6. Family h/o depression
7. Uncontrolled pain
8. Low socio-economic support
9. Social isolation
10. Significant loss
11. Drugs

Higher emotional distress is faced by the patients suffering from lung cancer in comparison to other cancers. The distress remains throughout the disease course, from diagnosis to treatment proper. The common psychiatric disorders that are encountered in lung cancer patients are anxiety disorders, depressive disorders, trauma and stress related disorders, cognitive impairment. Less common are bipolar disorders and psychosis.

Anxiety disorders.

Anxiety is the most common presentation after diagnosis of cancer. Anxiety may present as acute reaction to the diagnosis, or recurrence or treatment failure. It may be associated with depressive symptoms, lack of appetite, decreased sleep. The patients having premorbid anxiety issues may suffer more.

Treatment of anxiety disorders in lung cancer involves both pharmacological and non-pharmacological treatment. Pharmacological treatment includes antidepressants, antipsychotics, benzodiazepines. Drug choice should be made keeping the patient's medical illness in mind. Non-pharmacological treatment includes CBT, psychoeducation, MCP (Meaning centered psychotherapy), supportive psychotherapy.

Depressive disorders.

Depression is a common psychiatric co-morbidity in case of lung cancer and also a risk factor for suicide. The patients are vulnerable to depression at all stages of cancer. Identifying the early signs of depression and thus leading to early treatment, can improve the quality of life, treatment adherence and decrease the risk of suicide.[13]

The risk factors for depression and medical causes of depression have been summarized in Table 8A and Table 8B respectively.

Management of depressive disorders in lung cancer involves a comprehensive approach. A therapeutic alliance and recruiting family support are necessary before proceeding. A complete assessment and evaluation of medical illness should be done. The treatment of depression should be done along with the cancer treatment, thus relationship with the oncologist or radiotherapist should be maintained. The treatment involves both pharmacological and nonpharmacological strategies.

Table 8B: Medical causes of depression in lung cancer patients.

1. CNS Metastasis
2. Paraneoplastic syndrome [mainly SCLC]
3. Electrolyte disturbances
4. Systemic disorders like
   Autoimmune disorders
   Inflammatory disorders
   Infections
5. Endocrine abnormalities
   Hypothyroidism
   Adrenal insufficiency
6. Drugs
   Chemotherapeutic agents
   Steroids

Pharmacological Treatment.

The use of antidepressants in a cancer patient is challenging. The treatment warrants quick action, especially in the terminally ill patients, however the antidepressants take several weeks to act. The choice of anti-depressant should be made keeping in mind the patient's profile, medical illness, drug-drug interactions.

SSRI s are the first line drug used in the treatment of depression in cancer patients. They are generally well tolerated, have less drug-drug interactions, and not so toxic in overdose. SNRI s are newer class of antidepressants comprising of venlafaxine, desvenlafaxine and duloxetine. They are generally well tolerated with side effect profile like SSRI s. However, the effect on norepinephrine may result in palpitation and hypertension. Thus, blood pressure should be monitored regularly. TCA s are relatively older and less expensive than other antidepressants. However, they are better to be avoided in medical ill persons owing to their anti-cholinergic, anti-histaminic and anti-adrenergic side effects. Bupropion, a NDRI may have a mild stimulant effect owing to its action on dopaminergic system. This may be beneficial to cancer patients, specially having fatigue or psychomotor retardation. However, this should be used judiciously in patients with CNS metastasis because of risk of seizure disorders. Mirtazapine is also a good choice of anti-depressant in case of lung cancer patients. Its side effects of sedation and weight gain might be beneficial for cancer patients. It also has low drug-drug interactions.

Electroconvulsive therapy (ECT)

ECT is an effective treatment modality for depressed patients who has not responded to psychopharmacological treatment [at least trial of two antidepressant from different class with adequate dose and adequate time]. This can also be an option for patients having high suicide risk, side effect to antidepressant medicines, or cachexic patients. Though it is not an absolute contraindication to CNS metastasis, ECT should be used in these individuals with caution.

Psychotherapy

Several psychotherapeutic techniques are available for treatment of depressed cancer patients. They are often combined with pharmacological treatments. Supportive psychotherapy and CBT are among most used psychotherapies. Meaning cantered psychotherapy (MCP) is a

novel therapy that has been effective in improving depressive symptoms among advanced cancer patients. Group therapy is also useful (Flowchart 5).[14]

Flowchart 5: Meaning cantered psychotherapy (MCP).

It is based on Viktor Frankl's Logotherapy and Existential Analysis.

PHYSIOLOGICAL Self-awareness and Self-discovery.

Being vs Doing.

Existence – Body, Mind, Spirit

SAFETY Responsibility to self and others.

Confronting limitations

LOVE Experiences with others, nature, and arts. Creativity, Attitude

ESTEEM Creating a Legacy of Life Project

SELF ACTUALIZATION Meaning and purpose in life.

Attitude in suffering

SELF-TRANSCEDENCE;

SPIRITUAL DIMENSION

Suicide in lung cancer.

The incidence of suicide is higher in lung cancer patients in comparison to general population. It is important to address high risk patients and admit in psychiatric hospital if necessary (Table 9). Suicidal ideations should be considered from 4 perspectives-

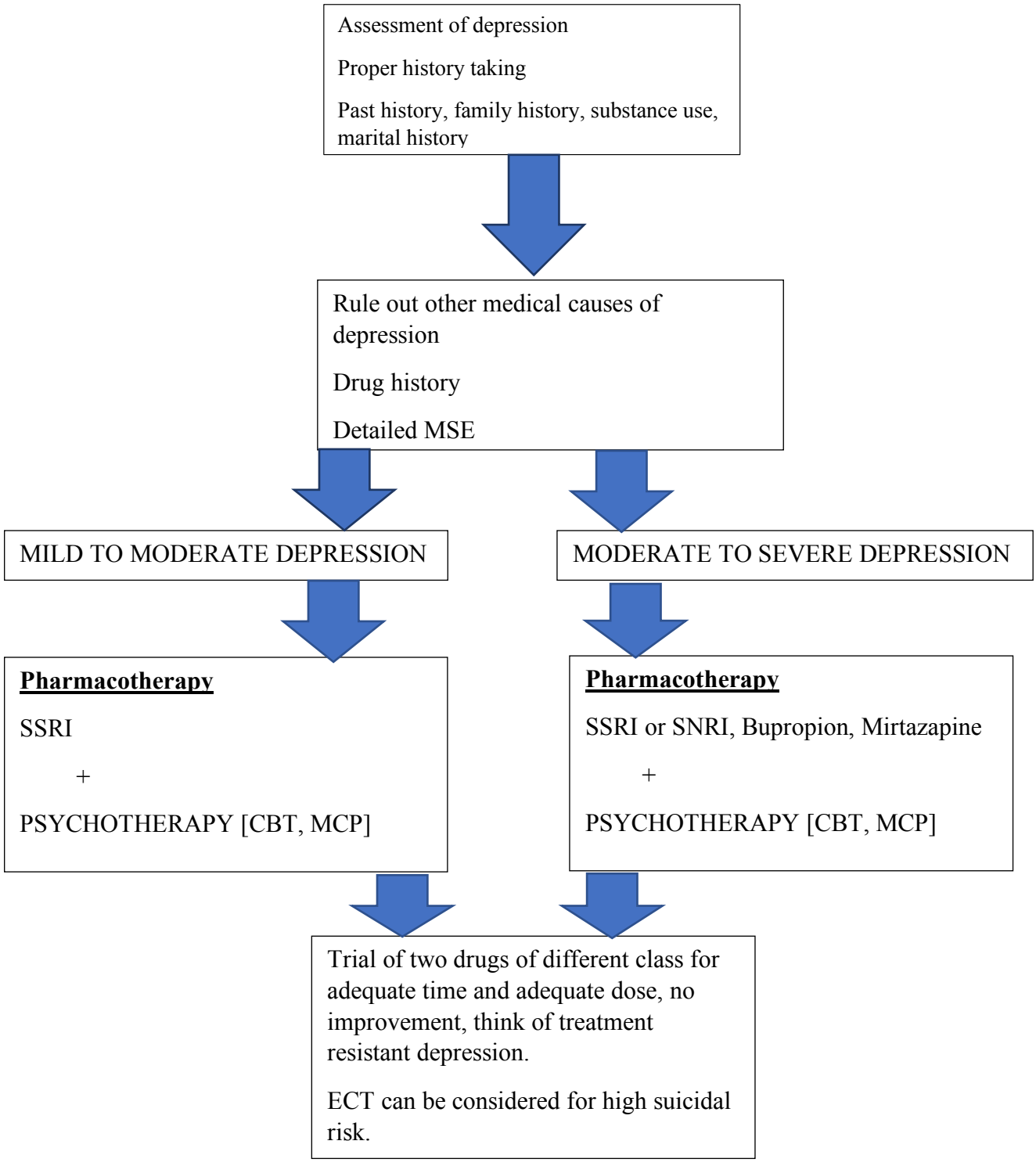
1. Suicidal thoughts occurring transiently in patients.
2. Suicidal thoughts in patients with good prognosis or in remission.
3. Suicidal thoughts in patients with poor prognosis.
4. Patients with terminal disease.

Table 9: Suicide risk factors in patients suffering from lung cancer.

1. Depression
2. Hopelessness
3. Uncontrolled pain
4. Extreme fatigue
5. Anxiety
6. Delirium
7. Substance abuse
8. Previous history of suicide attempt
9. Family history of suicide

The management of depression in lung cancer patients is very challenging which has been summarized in Flowchart 6.

Flowchart 6: Management of depression in cancer patients.



Cognitive impairment.

Delirium is one of the most serious neuropsychiatric complications encountered in any cancer patients. In case of lung cancer, the percentage of patient having delirium is relatively high (Table 10). If undertreated, delirium adds to morbidity and mortality of the cancer patients. It is a medical emergency and should be treated promptly.

Table 10: Causes of delirium in lung cancer patients.

1. DIRECT CAUSE
   CNS metastasis
2. INDIRECT CAUSE
   Hypoxia
   Metabolic encephalopathy
   Electrolyte imbalance
   Infection
   Paraneoplastic syndromes
   Treatment side-effects from chemotherapeutic drugs, steroids, opioids, anticholinergics, benzodiazepines
   Alcohol or drug withdrawal state

A number of scales have been developed to assess delirium including Delirium Rating Scale, the Confusion Assessment Method, the Memorial Delirium Assessment Scale [MDAS]. MDAS is a 10-item scale validated among hospitalized patients with advanced cancer. A cut-off score of 13 is diagnostic of delirium.

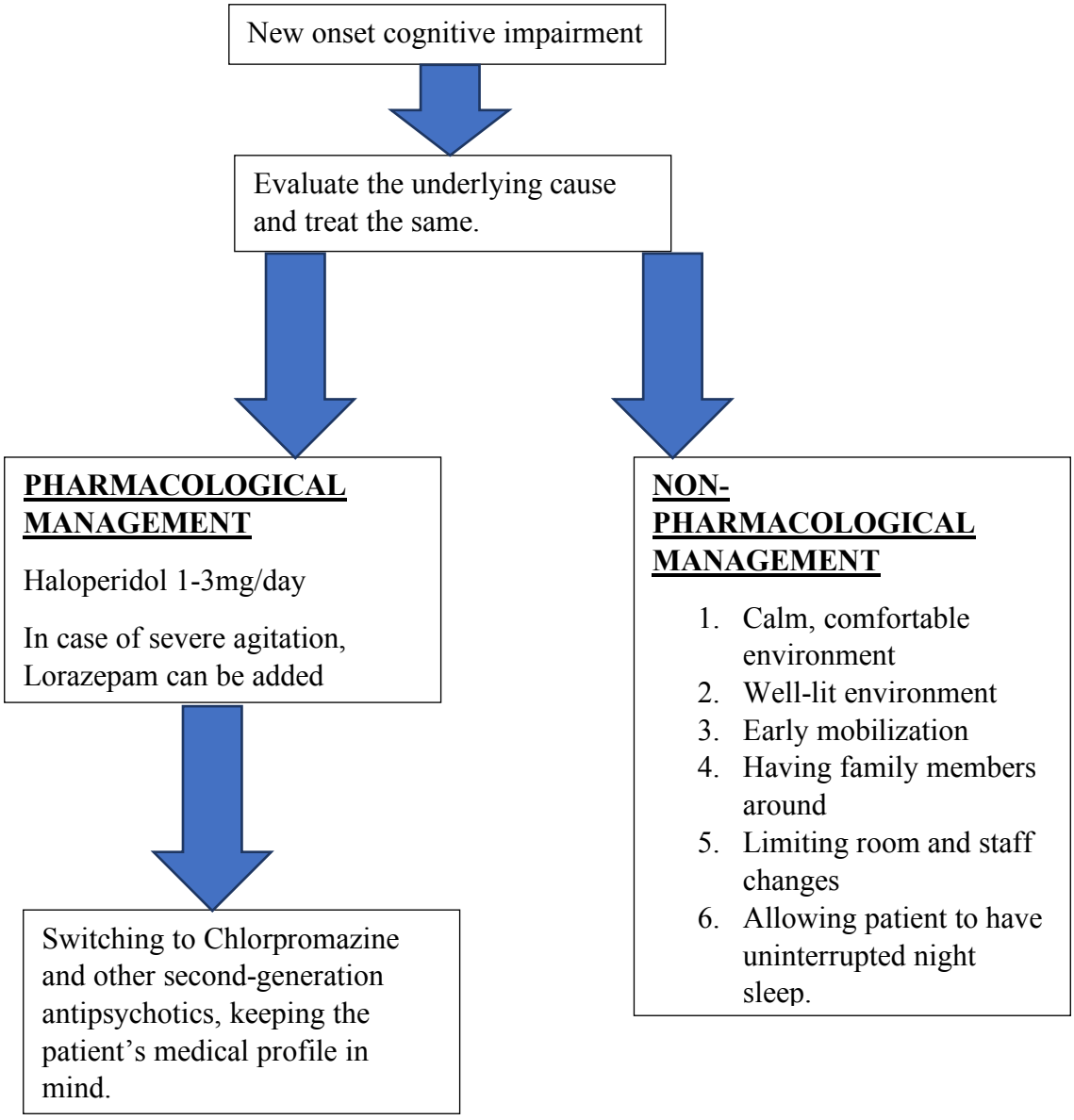
Treatment

The treatment approach to management of delirium includes evaluation and removing the offending cause. Symptomatic management includes both non-pharmacological and pharmacological treatment. Haloperidol is the gold standard in the treatment of delirium among cancer patients, due to its efficacy and safety profile. Other second-generation antipsychotics can also be used (Table 11). The management of delirium in lung cancer patients has been comprehensively summarized in Flowchart 7.

Table 11: Doses of antipsychotic drugs used in delirium.

DRUGS	DOSES
HALOPERIDOL	0.5-2mg every 2-12hrs
CHLORPROMAZINE	12.5-50mg every 4-12hrs
OLANZAPINE	2.5-10mg every 12-24hrs
RISPERIDONE	0.25-2mg every 12-24hrs
QUETIAPINE	12.5-200mg every 12-24hrs
ZIPRASIDONE	10-40mg every 12-24hrs
ARIPIPRAZOLE	10-30mg every 24hrs

Flowchart 7: Management of delirium in lung cancer patients.



Trauma and stress related disorders.

Trauma and stressor related disorders involve acute stress disorders, adjustment disorders and PTSD. This group of disorder is very common after the diagnosis of any cancer. Getting a diagnosis of cancer is perceived as a life-threatening event. All the three disorders are equally found after a diagnosis of lung cancer. Treatment involves early identification, crisis intervention, relaxation training. Support group may be helpful. Patients with more severe symptoms should be treated with antidepressants and anxiolytics.

Bipolar disorders.

Bipolar disorder in the cancer setting must be immediately referred to a psychiatrist owing to the complexity of treatment. The manic or violent patient must be calmed down as soon as possible as treatment of cancer needs a lot of co-operation from the patient side. Lithium should be used judiciously in case of cancer patients given its side effect profile. Lithium should be monitored in lung cancer patients with kidney disorder. SCLC type lung cancer can cause SIADH as a part of paraneoplastic syndrome. While using Lithium in such patient, occurrence of Diabetes Insipidus should be kept in mind. Ongoing medication, if the patient is a known case of bipolar disorder should be continued and monitored closely. Close liaison should be maintained with oncologist and radiotherapist.

Schizophrenia and psychosis.

Schizophrenia patients with lung cancer may give idiosyncratic meaning to the cancer symptoms and may tolerate them owing to their high pain threshold. Often, they are being diagnosed at a late stage. The ongoing medications should be continued along with the anti-cancer treatment. The side effect profile of the anti-psychotic drugs should be kept in mind.

COVID AND PSYCHIATRIC ISSUES

COVID 19 is a communicable disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2). The first case was detected in Wuhan province of China in November 2019. [15] Since then, it is the reason behind the ongoing global pandemic. It is discussed in detail in a separate chapter. We will just discuss about the general management of Covid and psychiatric illness.

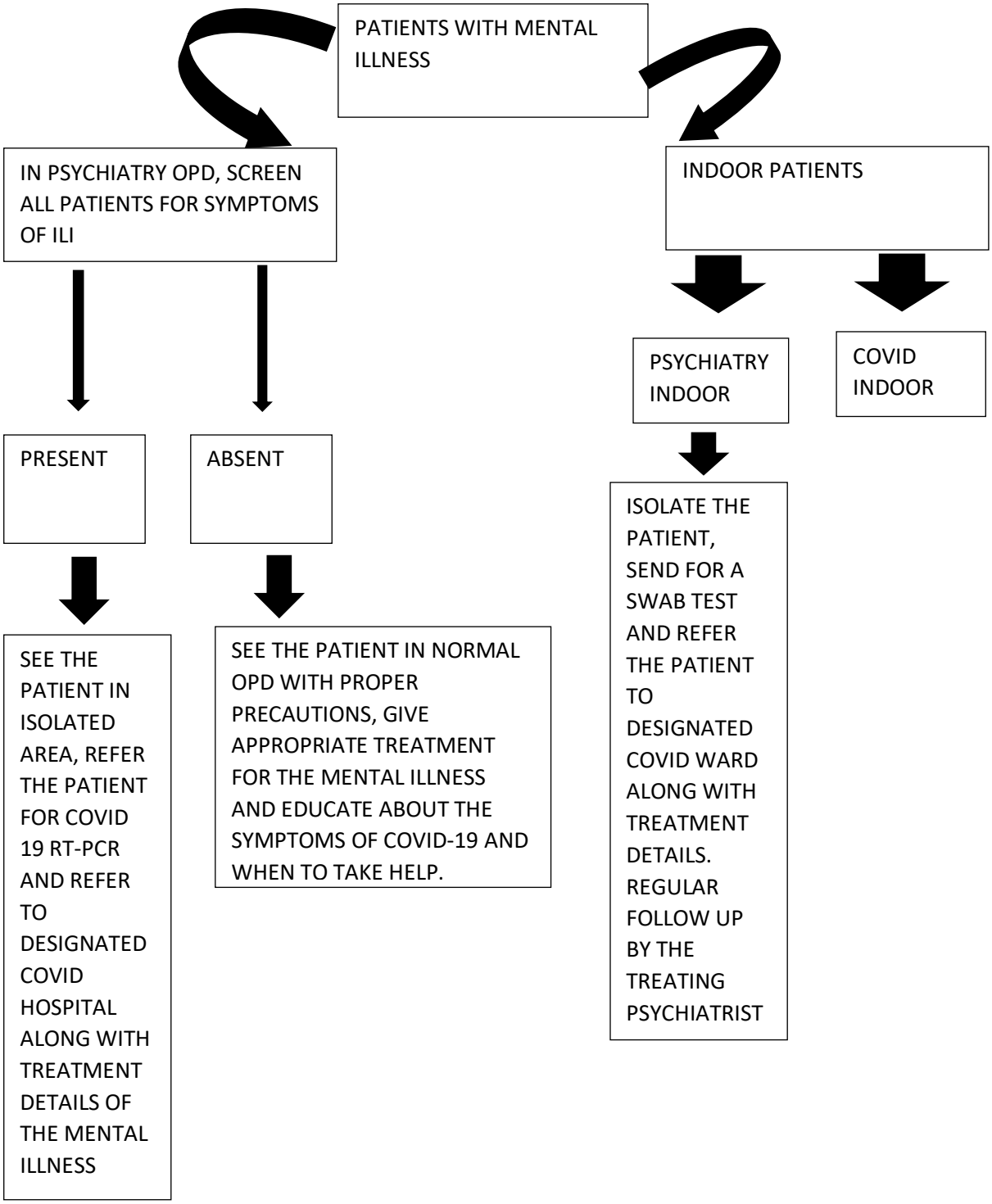
General management of psychiatric patients suffering from COVID 19.

The general psychiatric management of the COVID patients can be divided into two categories:

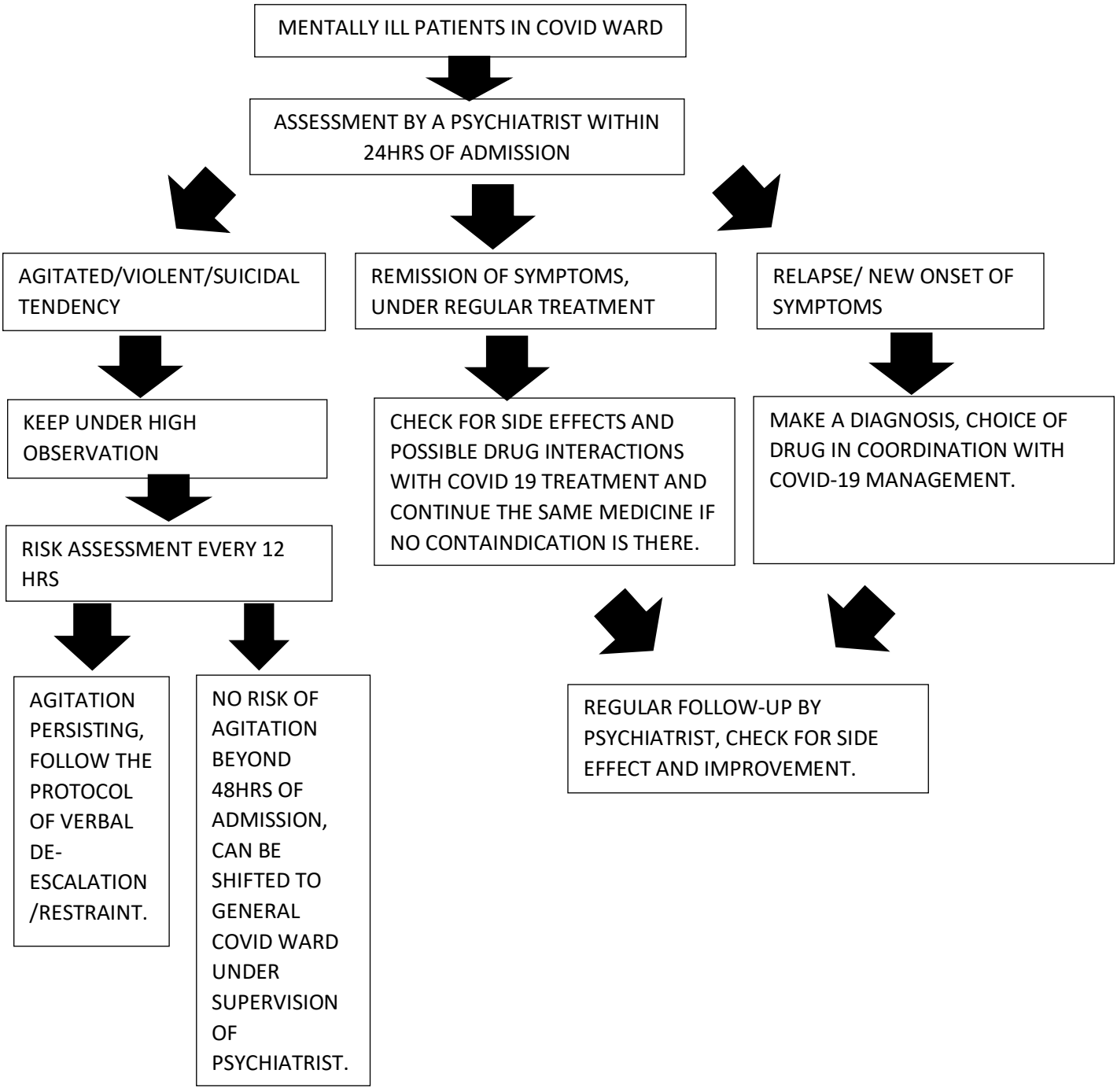
1. Patients already on psychotropic medications who is recently infected with COVID.
2. Covid patients developing new onset psychiatric complaints.[37]

The general management has been discussed in Flowchart 8 & 9.

Flowchart 8: Management of psychiatric patients developing COVID 19.



Flowchart 9: Management of mentally ill patients in COVID wards.



OBSTRUCTIVE SLEEP APNOEA (OSA)

Common psychiatric co-morbidities of OSA are depression, anxiety along with substance use disorders- tobacco and alcohol predominantly. Certain personality traits, eating disorders predispose to weight gain and indirectly to OSA, however direct bidirectional relationship of psychiatric disorders and OSA is controversial.

Continuous positive airway pressure (CPAP) is the first treatment of choice. Despite its well-recognized benefits including neuropsychological and depressive symptoms, CPAP acceptance and adherence remain problematic. Other alternative nonpharmacological treatments are oral appliances, weight loss, and surgery. Pharmacological agents could be useful adjuncts than main treatment.[16]

OSA and psychotropics

The atypical antipsychotics are deleterious in view of an induction of abnormal upper airway tone or alteration in respiratory control secondary to dopamine receptor antagonism. Induced obesity is another major concern.

Among the antidepressants TCA and SSRIs are useful in the context of decreasing REM quantity, leading to protection against respiratory-related arousals along with improving upper airway dilator tone through an increase in serotonin levels. Fluoxetine (increasing endogenous serotonin in the brainstem promotes upper airway dilation during the awake state) with Ondansetron (blocking peripheral serotonin release at 5-HT3 receptors) could be particularly advantageous. Mirtazapine, a mixed 5HT2 and 5HT3 antagonist has shown improvement in AHI (apnoea- hypopnoea index), however should be reserved for weight gain. Benzodiazepines are deleterious due to reduced upper airway muscle tone and decreased ventilatory response to hypoxia. However short-term use of nonbenzodiazepines like Zolpidem (reduction in sleep latency and mean arousal index) is associated with improved compliance to CPAP. In most guidelines, modafinil is recommended for use in patients who have residual daytime sleepiness despite optimal use of CPAP. Cardiovascular complications, dependency, and abuse potential are the issues need to be kept in mind.

Others

Smoking cessation is an important aspect of OSA as being a highly prevalent comorbidity. Interestingly nicotine may improve OSA by stimulating respiration and oropharyngeal muscles. Among the nicotine replacement therapies, chewing gum was found to be effective; transdermal patch did not show promising result. Alcohol intake prior to sleep is related to increase upper airway collapsibility. Alcohol related weight gain calls for strategic choice of Topiramate if adequately indicated. Cognitive behaviour therapy (CBT-I) may be a rational adjunct which is related to decreased suicidal ideation and depressed mood. The management of OSA with psychiatric comorbidities has been summarized in Table 12.

Table 12: Management of OSA with psychiatric comorbidities

Obstructive sleep apnoea.

(Points to remember)

Substance use- tobacco, alcohol; anxiety, depression are common comorbidities.

Healthy life style, weight loss, CPAP adherence- need to be emphasized.

Use of psychotropics should be rational.

Atypical antipsychotics cause increased upper airway tone, weight gain.

TCA, SSRIs are permissible. Fluoxetine with Ondansetron could be beneficial.

Short term use of Zolpidem is better than benzodiazepines.

Avoid long use or larger dose of stimulants.

NRT (Nicotine chewing gum) could be a good choice.

Topiramate could be a good choice for relapse prevetion.

CBT-I may be beneficial.

OCCUPATIONAL LUNG DISEASE

Occupational lung diseases are work-related, lung conditions that have been caused or made worse by the materials a person is exposed to within the workplace. It includes a broad group of diseases, including occupational asthma, industrial bronchitis, chronic obstructive pulmonary disease (COPD), bronchiolitis obliterans, inhalation injury, interstitial lung diseases (such as pneumoconiosis, hypersensitivity pneumonitis, lung fibrosis), infections, lung cancer and mesothelioma.[17] These diseases can be caused directly or due to immunological response to an exposure to a variety of dusts, chemicals, proteins, or organisms. Little is known about the prevalence of psychiatric disorders in occupational lung disease. Higher rates of depression and anxiety are related to the severity of dyspnoea and should be treated according to the disease. Delirium is also common in more chronic and severe form of diseases and should be treated accordingly.

HYPERVENTILATION SYNDROME OR PSYCHOGENIC DYSPNOEA

Hyperventilation syndrome or psychogenic dyspnoea is a common disorder that presents to emergency department very often. They may present with sudden onset shortness of breath, chest pain, dizziness, numbness or near syncope generally after a stressful event. Though before diagnosing, we need to eliminate other medical causes of dyspnoea.[18]

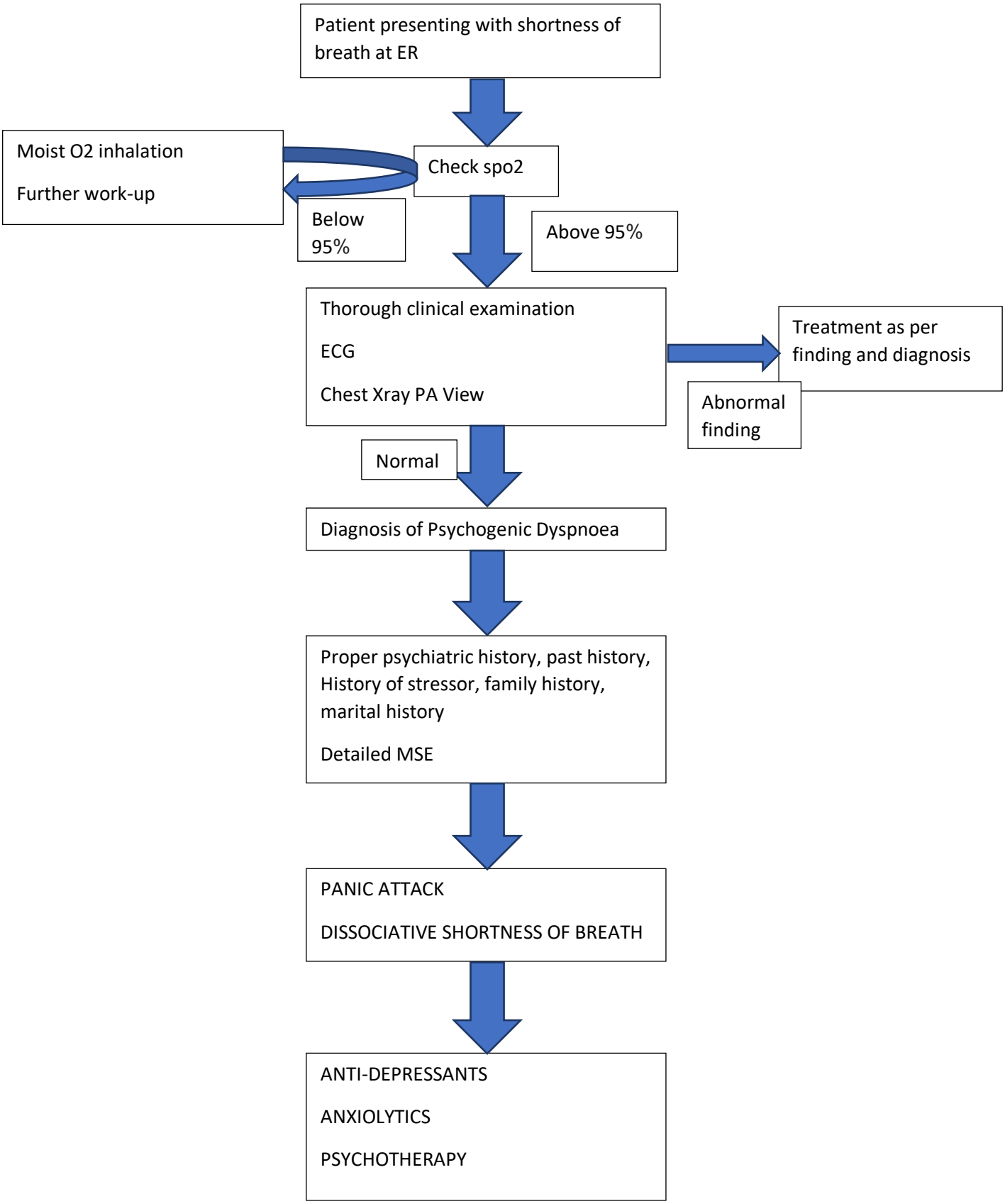
The necessary investigations and clinical work up should be done before proceeding for the treatment of psychogenic dyspnoea. Acute coronary syndrome and pulmonary embolism are acute emergencies which need immediate attention. A routine workup including pulse-oximetry, ECG, chest radiography should be done alongside clinical assessment (Flowchart 10).

Some common causes of dyspnoea have been summarized in Table 13

Table 13: Some common medical causes of dyspnoea.

1. Anaphylaxis
2. Acute exacerbation of asthma
3. Acute exacerbation of COPD
4. Acute coronary syndrome
5. Cardiac tamponade
6. Cardiac failure
7. Pulmonary embolism
8. Pneumothorax
9. Carbon monoxide poisoning
10. Upper airway obstruction
11. Broken ribs
12. Anemia

Flowchart 10: Approach to a patient presenting with hyperventilation syndrome.



PSYCHOTROPICS CAUSING RESPIRATORY SIDE-EFFECTS

The psychotropics causing respiratory adverse effects have been broadly summarized in Table 14.

Table 14: Psychotropics affecting respiratory system

Classification of drugs	**Drugs**	**Respiratory adverse effects**
Antidepressants	**Tricyclic antidepressants (TCAs)**	Adult respiratory distress syndrome, Pulmonary embolism, Pulmonary infiltrate, Respiratory depression
	Desvenlafaxine/Venlafaxine	Eosinophilic pneumonitis
	Duloxetine	Eosinophilic pneumonitis
	Mirtazapine	Can cause Aspiration pneumonia in toxic dose, as much as 5gm
1ST Generation antipsychotics (FGAs)	**Butyrophenones**	Dyspnoea, Pulmonary embolism, Pulmonary vascular disease
	Phenothiazines	Pulmonary embolism
2ND Generation antipsychotics (SGAs)	**Risperidone**	Dyspnoea, cough Rhinitis and Upper respiratory tract infection more common in paediatric population
	Quetiapine	Dyspnoea, cough, pharyngitis, rhinitis, nasal congestion
	Clozapine	Eosinophilic pneumonitis Can cause Aspiration pneumonia due to Sialorrhea
All FGA sand SGAs can rarely cause acute laryngeal dystonia.		
Mood stabilizers	**Lithium**	Very few case reports of Pulmonary hypertension
	Valproate	Rarely Diffuse alveolar haemorrhage or Interstitial pneumonitis
	Carbamazepine	Cough, dyspnoea, pulmonary infiltrate, interstitial pneumonitis, Hypersensitivity lung disorder
	Lamotrigine	Rhinitis rarely

Antiepileptics	**Phenytoin**	Cough, dyspnoea, Hypersensitivity lung disorder
	Topiramate	Upper respiratory tract infection, when used as monotherapy, 400mg/day Risk of non-anion gap metabolic acidosis, can cause hyperventilation
Acetyl-cholinesterase inhibitors	**Donepezil** **Rivastigmine** **Galantamine**	Can cause exacerbation of COPD rarely
Sedative-hypnotics	**Barbiturates** **Benzodiazepine**	Dyspnoea Respiratory depression in overdose
Beta adrenergic receptor antagonists		Wheezing, shortness of breath Acute exacerbation of asthma, COPD [less with beta1 selective drugs]
Anti-craving drugs	**Acamprosate**	Cough, rhinitis, dyspnoea [less severe but frequent]
Stimulant drugs	**Methylphenidate**	Dyspnoea, asthma, pulmonary infiltrate, interstitial pneumonitis, pulmonary vascular disease
Serotonin modulators	**Trazodone**	Dyspnoea, pulmonary infiltrates

RESPIRATORY DRUGS CAUSING PSYCHIATRIC SIDE-EFFECTS

The respiratory drugs causing psychiatric adverse effects have been summarized in Table 15.

Table 15: Drugs used in the respiratory unit causing neurobehavioral symptoms.

Classification of drugs	Drugs	Side effects
Antihistaminic	**1ST generation**	Drowsiness and Sedation
	2ND generation	No Known Psychiatric side-effects
Antitussives	**Narcotics**	Can cause Dizziness, drowsiness, sedation. Patient can get addicted; withdrawal symptoms may precipitate on stopping the drug.
	Non-narcotics	No specific psychiatric side-effects
Bronchodilators	**Beta 2 agonist**	Tachycardia, tremors; can mimic a panic attack
	Anticholinergics	Occasionally headache
	Xanthine derivatives	Headache, irritability, insomnia. Seizure and encephalopathy can occur in higher doses.
Leukotriene antagonist	**Montelukast**	Headache, dizziness
	Zafirlukast	Sleep Disorder Behavioural changes
Steroids	**Inhalational**	Less side-effect as systemic absorption is less
	Oral	Depression Mania Psychosis Anxiety Agitation Sleep Disturbances
Antitubercular drugs (ATDs)	**Rifampicin**	Potent inducer of CYP1A2, CYP2C19, CYP3A4. Reduce plasma levels of sertraline, nortriptyline, haloperidol, risperidone, clozapine.
	Isoniazid	CYP2C19, CYP3A inhibitor Documented toxicity with carbamazepine and benzodiazepines. Can cause Acute Psychosis.
	Pyrazinamide	No clear psychiatric side effects
	Ethambutol	No clear psychiatric side effects. To be cautiously used in renal impairment patients, and with the psychotropic drugs having renal toxicity.

Conclusion: The management of psychiatric illnesses in persons suffering from respiratory diseases require a comprehensive team approach. In liaison psychiatry, many a times the challenges have been thrown with an apprehension by non-psychiatrists that psychotropics in general are respiratory depressants. In the light of COVID 19 pandemic these clinical scenario has been dealt more frequently by mental health professionals as well as specialists from other fields. This guideline has been based on evidence based medicine supplemented by clinical experiences of the experts which can be used as a ready reckoner, keeping in the mind each case has its own merits and required to be dealt by situation based team approach for the benefit of the patient.

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TITLE: MANAGEMENT OF PSYCHIATRIC DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASES

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Clinical practice guideline

MANAGEMENT OF PSYCHIATRIC DISORDERS IN PATIENTS WITH CHRONIC KIDNEY DISEASES

Introduction

Chronic Kidney Disease (CKD) is a common public health problem involving all ages and significantly affects the body's overall homeostasis. It involves almost all organ systems and causes significant impairment in the quality of life. CKD is commonly caused by diabetes mellitus, hypertension, tubulointerstitial diseases, glomerulonephritis, polycystic kidney diseases, obstructive uropathy and congenital malformations of the kidney, etc.

In CKD, there is a progressive decline in kidney function. CKD often present with appetite loss, nausea, vomiting, easy fatigability, lethargy, muscle cramps, edema of the extremities, itching, disturbed sleep, increase in blood pressure, dyspnea, chest pain, alteration of urine output. There are five stages of CKD, and a significant number of cases do reach the advanced stage of CKD called end-stage renal disease (ESRD). At this stage, patients need renal replacement therapy (RRT), maintenance dialysis (peritoneal and/or hemodialysis), and/or renal transplantation (RT). As CKD affects the individual's functioning and produces significant disability, patients go through psychological distress. Evidence support that psychiatric comorbidities are common among patients with CKD [1]. The presence of psychiatric comorbidities in CKD affects the outcome of renal diseases as due to psychiatric comorbidity, these patients' help-seeking behavior, lifestyle, and medication adherence becomes poor, which attribute to poor outcomes. The psychiatric comorbidities associated with CKD are summarized in Table 1 below.

Table 1: Psychiatric comorbidities associated with CKD

Psychiatric comorbidities associated with CKD	**Prevalence**
• Depression [2]	Advanced CKD: 22.8% CKD stage 1 to 5: 21.4% Recipients of Kidney transplant: 25.7%
• Anxiety [3]	Stage 3 to 5 CKD: 24.8% to 34.3% Renal transplant patients: 26.6%
• Cognitive impairment[3]	Advanced CKD and hemodialysis patients: Up to 60%

Patients with CKD often present with various psychiatric disorders. The psychiatric disorders commonly seen in patients with renal diseases are depression, anxiety disorders, and delirium [4]. Patients with ESRD go through enormous distress due to their compromised health, dependence on others, regular, frequent dialysis, continued cost of treatment, the uncertainty of renal transplant, which increases their vulnerability for mental illness. Metabolic derangements (electrolyte imbalance), anemia, renal bone disease, and hypertension associated with renal diseases also contribute to psychiatric morbidities like depression and anxiety [4]. Similarly, several medications like – amantadine, aspirin, ciprofloxacin, steroids, phenytoin may contribute to the development of psychiatric manifestations ranging from anxiety, depression, insomnia to psychosis and delirium [4]. Use of these medications (whenever indicated) in patients with CKD and RRT needs absolute caution. Evidence supports that comorbid depression adversely affects the attitude towards medication compliance and compromises sleep quality [5].

Similarly, research suggests that patients with ESRD undergoing peritoneal dialysis and hemodialysis have deficits in cognitive function compared to the general population [6,7]. The deficits in cognition are evident in the domains of attention, concentration, orientation, and executive functions [7]. Similarly, reduced serum albumin level in patients with dialysis is associated with a decline in delayed memory, visuospatial skills, language ability, and general cognitive function [6].

This paper focuses on the management of psychiatric disorders in CKD with a specific focus on pharmacological management. Prescribing treatments to patients with renal diseases and those with renal replacement therapy (RRT) need certain careful considerations (Table 2).

Table 2: Considerations while prescribing psychotropic medications in patients with renal diseases and those with renal replacement therapy (RRT)
• Interaction of psychotropic drugs with medications used for renal diseases • Alteration of renal physiology and other metabolic parameters • Impact of psychotropic medications on renal function • Impact of decreased renal function on the therapeutic efficacy of psychotropic medications • Dialysis clearance of the psychotropic medications • Interaction of psychotropic medications with the immunosuppressants used in patients with RRT

Renal physiology relevant for psychiatry

Optimal renal function is required for maintaining homeostasis in the body. Renal function is required for the excretion of waste products from the body. Glomerular filtration rate (GFR) gives an estimation of renal function. GFR can be measured by checking ideal filtration markers, creatinine clearance, and Cystatin C protein [8]. Creatinine clearance test is considered as a marker of renal functioning. In a normally functioning kidney, the creatinine clearance is >60ml/minute; but, there are variations in the normal value of GFR among males and females (males > females), across different age groups and among different races [9,10]. Because of the cumbersome nature of the measurement of GFR, GFR is now more commonly estimated by using various formulas, which have been validated in many ethnic groups. The two most commonly used formulas for eGFR are *Modification of Diet in Renal Disease* (MDRD) and *CKD-Epidemiology Collaboration* (CKD-EPI) [11,12]. The severity of renal disease is broadly classified into five stages based on GFR; stage 1-eGFR ≥ 90 ml, stage 2-60-89 ml/min, stage 3-30-59 ml/min, stage 4-15-29 ml/min and stage 5-< 15 ml/min. [13]. In renal diseases, the protein binding ability of the psychotropic medications is decreased. As the unbound (free) forms of medications are responsible for the

therapeutic effect and side effects, there is a need for dose adjustment in renal diseases, depending on the decrease in renal function [9]. Renal diseases also cause impairment in the excretion of certain psychotropic drugs and their metabolites that have renal excretion [8]. The formula for estimating the GFR[12] are:

1. The MDRD formula

$$GFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

2. The CKD-EPI formula

GFR = 141 × min (Scr /κ, 1) α × max (Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where: Scr: Serum creatinine in mg/dL,

κ: 0.7 (for females); 0.9 (for males)

α: -0.329 (for females); -0.411 (for males)

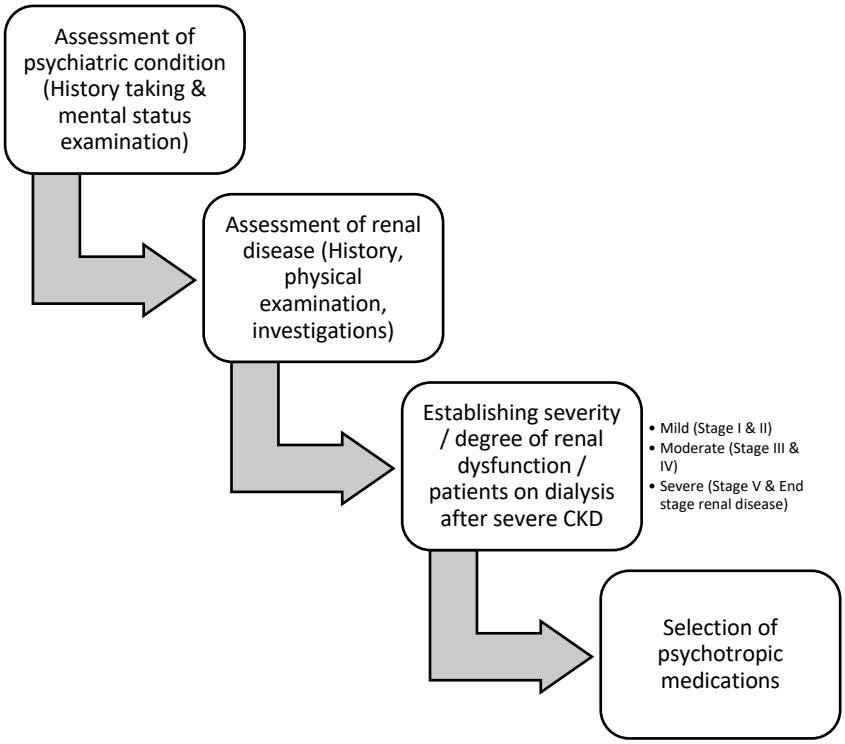
Min: Minimum of Scr /κ or 1

Max: Maximum of Scr /κ or 1

Assessment of psychiatric disorders in patients with CKD and RRT

Patients with CKD and RRT having psychiatric illnesses need to be assessed thoroughly. The figure 1 below demonstrates the sequential clinical assessment that is relevant for considering appropriate psychotropic medications.

Figure 1: Flow diagram showing assessment of patients with psychiatric illnesses with renal diseases



Psychiatric disorders in patients with CKD and RRT

Psychiatric disorders are commonly seen in patients with CKD, on dialysis, and renal transplants (Table 3).

Table 3: Common psychiatric disorders in patients with CKD and RRT
1. Psychosis 2. Mood disorder 3. Anxiety disorder 4. Neurocognitive disorders 5. Substance use disorders 6. Childhood psychiatric disorders 7. Others like sleep disorders, psychosexual disorders

I. Prescribing antipsychotic drugs in patients with CKD and RRT

Antipsychotic medications are the mainstay treatment modality for the management of psychosis. Though the kidney excretes few first-generation antipsychotic medications as inactive metabolites, most first-generation antipsychotics are safe in CKD and do not require dose adjustment [9]. Among the first-generation antipsychotic medications, haloperidol is safest. The phenothiazine group of antipsychotic medication increases the risk of hypotension in patients with CKD [9]. Similarly, most second-generation (atypical) antipsychotic medications are also considered safe in renal diseases as most of them are metabolized in the liver [9]. Among the atypical antipsychotics, paliperidone is excreted by the kidney in unchanged form, whereas olanzapine, risperidone, quetiapine, clozapine, and iloperidone are excreted by the kidney as their metabolites [9]. Amisulpride needs to be avoided in ESRD [8]. There is little evidence regarding any risk of worsening renal impairment or toxicity due to the metabolite with the use of aripiprazole in patients with CKD. However, it is recommended to avoid using depot preparations of aripiprazole in ESRD [8]. No evidence suggests dose reduction of asenapine till severe renal impairment; however, the use of asenapine in ESRD is poorly studied, hence better to be avoided in this condition [8].

Most antipsychotic medications are safe in mild to moderate renal dysfunction. Dose adjustment may be required in severe to ESRD [9]. Caution needs to be exercised while using antipsychotic medications like chlorpromazine, clozapine, flupentixol, haloperidol, lurasidone, olanzapine, risperidone, quetiapine, paliperidone, ziprasidone, pimozide, trifluoperazine, and zuclopenthixol [8]. In renal impairments, long-acting (depot) preparations of all typical and atypical antipsychotic medications need to be avoided [8].

Some evidence supports that severe mental illnesses (e.g., schizophrenia and bipolar affective disorder) increase CKD risk, and the antipsychotic medications and mood-stabilizing anticonvulsants also increase the chance of renal impairment [8]. Hence, adequate caution needs to be exercised while treating these patients.

II. Prescribing anticholinergic drugs in patients with CKD and RRT

Patients with psychotic illnesses receiving antipsychotic medications often have extrapyramidal side effects. Anticholinergic medications like trihexyphenidyl and procyclidine are commonly used for the treatment of extrapyramidal side effects. However, using these anticholinergic

medications may cause urinary retention and need to be avoided in conditions with obstructive genitourinary conditions [14].

III. Prescribing antidepressant drugs in patients with CKD and RRT

Patients with renal diseases with depression need to be treated with special precaution. Antidepressant treatment, psychotherapy, and somatic treatments are commonly used in the treatment of depression. Cognitive behavior therapy (CBT) is a commonly practiced and evidence-based psychological treatment for the management of depression. A recent meta-analysis supports the efficacy of cognitive behavior therapy in the management of depression in patients with renal diseases on dialysis [15].

Antidepressant medications are often metabolized in the liver and excreted by the kidney [9]. Among the selective serotonin reuptake inhibitors, fluoxetine level remains unchanged irrespective of the severity of renal impairment, whereas paroxetine concentration goes high in patients with severe renal impairment requiring dose adjustment [9]. Citalopram use increases the risk of sudden cardiac arrest when used in patients undergoing hemodialysis. The risk is significantly higher in comparison to other selective serotonin reuptake inhibitors [8]. Among the serotonin-norepinephrine reuptake inhibitors, venlafaxine and desvenlafaxine excretion are affected by renal impairment. In severe renal impairment, the plasma concentration of these medications may increase up to 50%; hence, there is a need for dose reduction [9]. However, duloxetine is safe in mild to moderate renal impairment. Severe renal impairment increases the blood level of duloxetine multi-folds requiring dose reduction [9]. Though the safety profile is acceptable for tricyclic antidepressants, monoamine oxidase inhibitors, and bupropion in mild to moderate renal diseases, dose reduction and slow titration is required for severe renal impairment [9]. Approximately three fourth of the mirtazapine is excreted by kidneys in unchanged form, and renal impairment causes a decrease in the excretion of the drug, increasing plasma concentration [8]. Therefore, dose reduction is required in CKD. Vortioxetine is safe in renal disorders as the existing evidence suggests that it is minimally excreted by the kidney; however, caution needs to be followed during its use in patients with ESRD [8]. Vortioxetine is a new molecule and requires extensive research for safety. Hence, the clinician should exercise adequate caution and need to be

watchful for all possible side effects, while recommending vortioxetine in patients with CKD and RRT.

Tricyclic antidepressants like amitriptyline, nortriptyline, imipramine, clomipramine, due to their anticholinergic property, may cause urinary retention, postural hypotension, sedation, and confusion like state [8]. Agomelatine has negligible renal excretion, so believed to be safe in early renal diseases; however, caution needs to be exercised in moderate to severe renal impairments [8]. Likewise, caution needs to be exercised while using dosulepin (Dothiepin) as the majority of the active metabolites of the drug are excreted through the kidney, and renal impairment causes accumulation of the metabolites resulting in excess sedation [8]. Therefore, it has been recommended that patients with GFR less than 20ml/minute need to be given low doses with slow escalation [8]. Trazodone also needs to be used in low doses to manage depression in patients with CKD [8].

IV. Prescribing mood stabilizers in patients with CKD and RRT

Mood stabilizers are the mainstay of treatment in the management of bipolar affective disorder. Mood stabilizers that are effective in managing manic episodes are lithium, valproate, carbamazepine, and oxcarbazepine, whereas for the management of depressive episodes in bipolar affective disorder, lithium and lamotrigine are found to be useful. There is a need for dose adjustment for lithium in mild to moderate renal impairment. Lithium use needs to be avoided, preferably in patients with severe renal diseases and ESRD [9]. Lithium is also known to produce renal disease, primarily tubulointerstitial damage. Therefore, patients receiving lithium treatment need to be regularly monitored for serum lithium levels and renal function tests in regular intervals.

Valproate (or Valproic acid) is a commonly used antiepileptic medication, which also has significant mood-stabilizing properties [16]. However, valproate needs to be used cautiously in patients with renal impairment and urea cycle disorders [16,17]. Evidence suggests that valproate may cause renal tubular injury and Fanconi's syndrome [17]. Lamotrigine is another mood stabilizer commonly recommended in the management of bipolar depression. Inactive metabolites of lamotrigine are excreted by the kidney; hence there is no need for dose adjustment [9]. The data regarding the use of lamotrigine in severe renal diseases and ESRD are sparse. Dose titration may be required in such a group of patients and patients on dialysis [9]. Oxcarbazepine is metabolized

by glucuronidation. Its subsequent metabolites are excreted through the kidney. Mild to moderate renal impairment does not require dose adjustment for oxcarbazepine; however, for severe renal impairment and ESRD, dose reduction of oxcarbazepine (maybe by 50% of the recommended dose) is required [9].

V. Prescribing anxiolytic drugs (benzodiazepines & non-benzodiazepine anxiolytics) in patients with CKD and RRT

Anxiety is a common comorbidity among patients with CKD, patients on dialysis, and following renal transplant. Persistent anxiety that is significantly impairing and lasts beyond a specific time period is considered an anxiety disorder. Various pharmacological and non-pharmacological treatment options are considered in patients with anxiety disorders. Among the pharmacological treatment options, antidepressants, benzodiazepines, beta-blockers, and buspirone are commonly used [18]. The active metabolites of buspirone are excreted by the kidney. In Mild to moderate renal impairment, it should be started in a low dose with slow escalation; but, it needs to be avoided in severe renal impairment [8]. Among the benzodiazepines, chlordiazepoxide, diazepam, clonazepam, lorazepam, nitrazepam, oxazepam need to be used with caution as their active metabolite may accumulate in renal impairment, causing excessive sedation [8]. Gabapentin and pregabalin are excreted by the kidney in unchanged form; hence, dose reduction is required in renal impairment [8]. Promethazine is an antihistaminic agent with anxiolytic properties. Therefore, it needs to be used with caution as it may produce excessive sedation in renal impairment [8]. Antidepressant medications are commonly used in the management of anxiety disorders. The precautions that needed to be exercised have been discussed in detail under the section on the treatment of mood disorders in renal impairment (above).

VI. Prescribing pro-cognitive drugs in patients with CKD and RRT

Neurocognitive disorders like dementia are commonly seen in the elderly population. Alzheimer's disease is a common neurocognitive disorder in the elderly. Medications with anticholine esterase

properties like donepezil, rivastigmine, and galantamine are commonly used in patients with dementia. Memantine is an antiglutamatergic drug also used in the treatment of dementia.

The commonly used antidementia medication, donepezil, is partially excreted by the kidney in unchanged form; however, its clearance is not much affected in renal impairment [8]. Galantamine gets excreted by the kidney, partially. Dose reduction is recommended beyond severe renal impairment [8]. ESRD is a contraindication for the use of galantamine [8]. It has been recommended to start with a low dose and go slow to use memantine and rivastigmine to manage dementia in CKD [8].

VII. Prescribing drugs used in addiction management in patients with CKD and RRT

Patients with CKD may have comorbid substance use disorders. Anti-craving agents like acamprosate, naltrexone, and baclofen are used in the management of alcohol use disorder. Benzodiazepines remain the mainstay of treatment of withdrawal symptoms of alcohol. Disulfiram is used as a deterrent in the management of alcohol use disorder. Similarly, buprenorphine and methadone are commonly used in the management of opioid use disorders. Naltrexone is used as a treatment modality for relapse prevention, being an opioid receptor antagonist. Bupropion is used as an anti-craving agent for tobacco. The precautions regarding the use of bupropion and benzodiazepines have been mentioned earlier in this article.

The kidney excretes Acamprosate in an unchanged form. However, CKD may cause impairment of excretion of acamprosate and an increase in its plasma concentration [19]. Therefore, Acamprosate may be used in lower doses for patients with mild to moderate renal impairment and avoided in severe renal impairments and ESRD [20]. For moderate renal impairment, the recommended starting dose of acamprosate is 333mg, one tablet thrice in a day [21].

Naltrexone has an important role in the management of alcohol use disorder and opioid use disorder. The kidney majorly excretes naltrexone and its primary metabolite. There is a lack of adequate studies on naltrexone in severe renal impairment; however, caution needs to be taken while prescribing naltrexone in severe renal impairment and ESRD [22].

Buprenorphine is primarily metabolized and excreted by the liver. There is no alteration of pharmacokinetics of buprenorphine in patients on hemodialysis. Hence, dose alteration of buprenorphine is not required in patients with CKD, irrespective of their severity [23].

Methadone and its metabolites are excreted by the kidney to some extent. However, the safety of methadone use among patients with renal impairment is not systematically studied. Hence, it is recommended to use methadone cautiously in renal impairment patients. It is advisable to start with a low dose and give methadone with less frequent dosing [24]. The pharmacokinetics of baclofen in CKD is not well studied. It has been suggested for dose reduction of baclofen in renal impairment. Dose reduction is required more as the severity of renal impairment increases [25]. Similarly, dose reduction is also recommended for disulfiram used to manage alcohol use disorder with renal impairment [26].

VIII. Prescribing drugs in the management of childhood psychiatric disorders in patients with CKD and RRT

Children and adolescents are also affected by CKD. Many psychiatric disorders like autism, attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder, conduct disorder are commonly diagnosed at an early age (childhood and adolescence). The pharmacological management in autism, oppositional defiant disorder, and conduct disorder has a limited role. If pharmacotherapy is recommended for the aggressive and disruptive behavior due to the above condition, mostly mood stabilizers, antipsychotic medications, or antidepressant medications are prescribed. The precaution to these medications in CKD has been mentioned in the above sections. The same strategy of start low and go slow should be followed with regular monitoring for the side effects.

Patients with ADHD are often treated with stimulants like methylphenidate, atomoxetine, dextroamphetamine, and modafinil. No data is available regarding the use of dextroamphetamine and modafinil in CKD and patients on dialysis [27]. However, caution must be exercised with close monitoring for side effects when these medications are given in severe renal impairment and ESRD. Though no dose adjustment is suggested for the use of methylphenidate in CKD, adequate caution must be taken while prescribing it to patients on dialysis [27]. The kidney excretes the metabolites of atomoxetine, and cautious use of atomoxetine is recommended in treating ADHD in CKD [28].

IX. Prescribing sedative & hypnotic drugs in patients with CKD and RRT

Sleep disturbances are common among patients with CKD. Conventionally, benzodiazepines, zolpidem, eszopiclone, tricyclic antidepressants, mirtazapine, and melatonin are used to treat insomnia. Adequate precaution needs to be exercised while using benzodiazepines, tricyclic antidepressants, and mirtazapine in patients with CKD, as mentioned above (under antidepressant and anxiolytic section). The kidney minimally excretes eszopiclone and zopiclone; so, no dose adjustment is required. Similarly, though the clearance of zolpidem is moderately reduced for zolpidem, dose reduction is not usually required in patients with renal impairment [8].

X. Prescribing drugs used in management of psychosexual disorders in patients with CKD and RRT

Men with CKD may have sexual dysfunctions like premature ejaculation and erectile dysfunction. Selective serotonin reuptake inhibitors are commonly used in the treatment of premature ejaculation. Adequate precautions need to be exercised (as mentioned above under the mood disorder section) while using selective serotonin reuptake inhibitor for premature ejaculation. Phosphodiesterase inhibitors like sildenafil and tadalafil are used in the management of erectile dysfunction. Sildenafil is to be used with caution in patients with renal impairment. Severe renal impairment warrants a dose reduction of sildenafil. A low dose (25mg) may be considered the starting dose of sildenafil for erectile dysfunction in severe renal impairment [29]. Research evidence is poor concerning tadalafil, though theoretically, it seems to be a safer option than sildenafil [30]. However, a recent trial suggests the safety of low dose tadalafil in treating erectile dysfunction in ESRD patients undergoing hemodialysis [31]. Hence, caution and dose reduction need to be exercised, while using tadalafil in CKD patients, particularly those with ESRD. Similarly, behavioral and other psychological treatment measures need to be prioritized for patients to address their sexual difficulties, rather than relying more on pharmacotherapy [32].

Specific considerations regarding the use of psychotropic medications in RRT

There is some uniqueness with regards to patients on RRT, which are [33,34]:

1. Patients planned for RRT or who had undergone RRT have ESRD

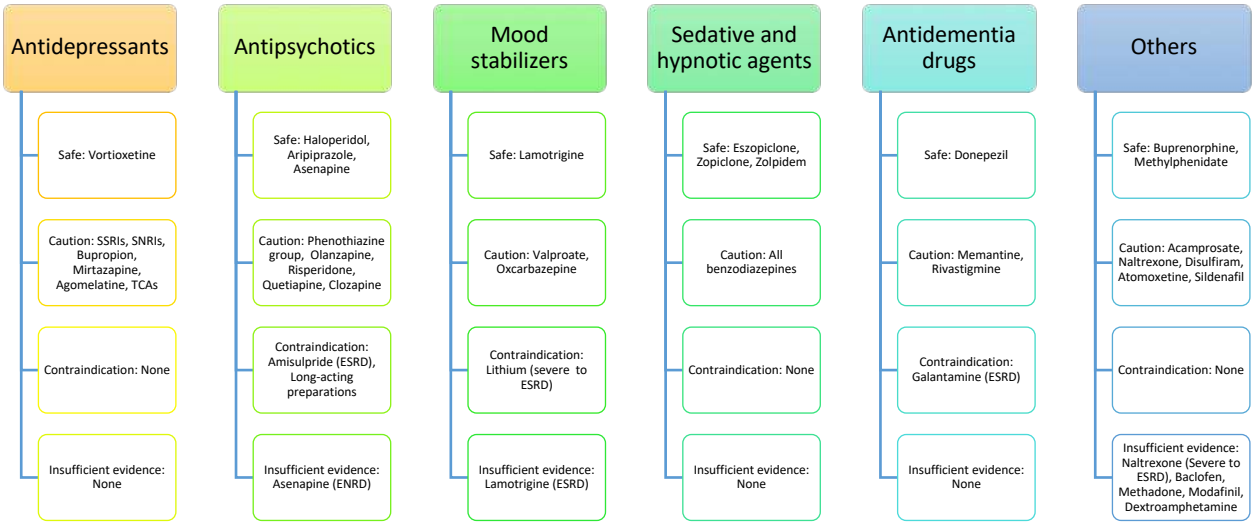
2. Patients who had undergone renal transplant remain on life-long immunosuppressants

Patients with renal transplants receive immunosuppressant agents like – prednisolone, tacrolimus, azathioprine, cyclosporine, mycophenolate, and rapamycin [33,34].

Patients receiving immunosuppressants need to avoid monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants. In addition, selective serotonin reuptake inhibitors and selective serotonin and norepinephrine reuptake inhibitors need to be used with caution as drugs like fluoxetine, paroxetine, and fluvoxamine inhibit the CYP 3A4 enzyme in the liver and increase the plasma level of calcineurin inhibitors like tacrolimus and cyclosporine [35]. Antidepressants relatively safe to use in renal transplantation patients are escitalopram, sertraline, citalopram, venlafaxine, mirtazapine, and bupropion [35].

Valproate and carbamazepine are the CYP 3A4 enzyme inducers. The use of these medications decreases the concentration of sirolimus and everolimus, which can increase the risk of graft rejection [36]. Other drugs like modafinil, armodafinil, phenobarbital, topiramate, and clobazam were also found to induce CYP 3A4 and, therefore, reduce the activity of calcineurin inhibitors [37]. The use of mycophenolate along with antipsychotic medication clozapine increases the risk of blood dyscrasia [37]. Summary of the safety of common psychotropic medications in CKD has been discussed in table 4 below.

Table 4 Summary of safety of common psychotropic medications in CKD.



Lower urinary tract diseases and use of psychotropic medications

Lower urinary tract diseases include diseases of the bladder and beyond. Of these, benign prostatic hyperplasia (BPH) is a common age-related pathology of the prostate in males. BPH obstructs the bladder outflow by compressing the urethra. Psychotropic medications like antipsychotics (e.g., chlorpromazine, quetiapine), antidepressants (e.g., tricyclic antidepressants, milnacipran, fluoxetine, citalopram), anticholinergic agents (e.g., trihexyphenidyl, Procyclidine, promethazine), anticonvulsants have the potential to cause urinary retention [38]. The safer psychotropic medications to be used in BPH are-

- Antipsychotics: Haloperidol, Amisulpride, Olanzapine, Aripiprazole
- Antidepressants: Bupropion, Sertraline, Agomelatine, Desvenlafaxine
- Mood stabilizer: Lithium, Valproate, Carbamazepine, Lamotrigine

Principles of psychotropic drug modification during CKD and RRT

Certain general recommendations have been prescribed while using psychotropic medications in patients with renal diseases and renal transplantation. Table 5 below summarizes the recommendations[8].

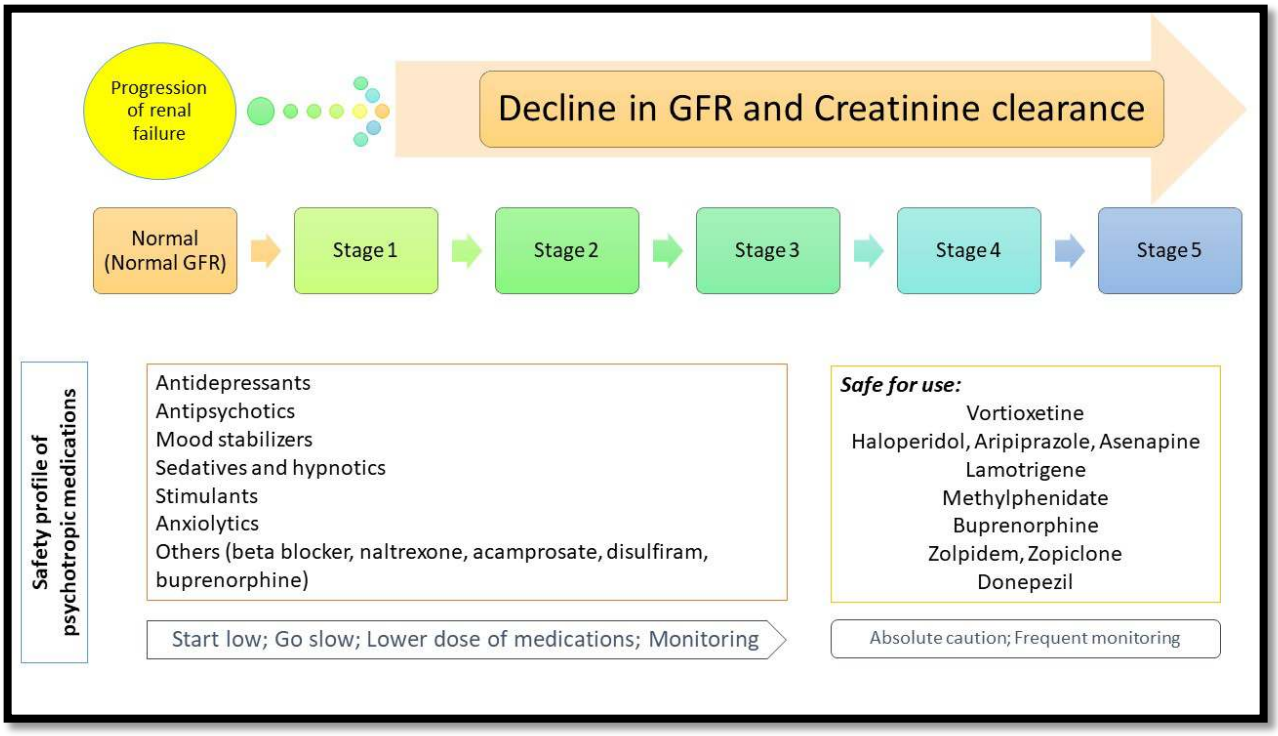
Table 5: General Recommendations for psychotropic use in CKD

General principles of psychotropic medication use among patients with CKD [8]
1. Choose appropriate medication considering the degree of renal impairment
2. Monitor the renal function and electrolytes regularly
3. Avoid medications with nephrotoxic effects
4. Exercise cautions for drugs that get excreted renally (particularly in beyond moderate degree of renal impairment)
5. All elderly (>65 years) needs to be evaluated routinely for renal function periodically.

6. Follow the principle of "Start low and go slow."
7. Avoid polypharmacy
8. Depot preparations of the psychotropic medications need to be avoided
9. Side effects of the psychotropic drugs need to be monitored closely (Serotonin syndrome with antidepressants, extrapyramidal side effects with antipsychotic medications)
10. Avoiding medications that prolong QTc interval and medications that can cause urinary retention (medications with anticholinergic properties)

In addition to these general recommendations, patients on dialysis may need supplementation of drugs after dialysis for drugs which are dialysable. This area is out of the scope of this review. However, treating doctors should consult recommendations for specific drugs for a type of dialysis; hemodialysis, peritoneal dialysis, or continuous renal replacement therapy (CRRT) and supplement drugs if required. Figure 2 below summarizes the safety profile of various psychotropic medications in various stages of CKD.

Figure 2: Safety profile of common psychotropic medications in various stages of CKD



Conclusion

A collaborative work between the nephrologist and psychiatrist is required to better the patients of renal diseases with mental health issues. The use of non-pharmacological measures like psychotherapy (Cognitive behavior therapy, behavior therapy, relaxation techniques) and somatic treatments like electroconvulsive therapy, transcranial magnetic stimulation, and transcranial direct current stimulation may be helpful in patients with chronic renal diseases and those with RRT.

Similarly, the clinician needs to consider the potential interactions of the psychotropic medications with the immunosuppressants used in patients with renal transplants. The selection of appropriate psychotropic agent in appropriate doses in patients with CKD and RRT will minimize the harm and maximize the benefit.

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Management of psychiatric disorders in patients with hepatic and gastrointestinal diseases

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Abstract
There is an increased prevalence of psychiatric disorders among the medically ill. Though the principles of psychopharmacological treatment among medically ill remain consistent across medical and surgical specialties, many physicians and even psychiatrists feel ill-equipped to prescribe for such patients due to concerns about safety, efficacy, and drug-drug interactions. More pertinently, this may lead to underdiagnosis and undertreatment with adverse consequences for the patient. In this guideline, we outline general and specific considerations when prescribing psychotropic drugs for those with liver and gastrointestinal dysfunction with a focus on drug selection, pharmacokinetic changes, and dosing recommendations. This document will serve as a clinical manual and ready reckoner for specialist and non-specialist physicians prescribing psychotropic drugs for those with a range of hepatic and gastrointestinal diseases.

1 Introduction

Psychiatric disorders and general medical conditions share a bidirectional relationship. Patients with severe mental illness have an increased prevalence of concurrent medical conditions and chronic medical illness also increases risk of developing mental illness. Psychotropic agents are commonly used in management of psychiatric disorders in the medically ill. Co-morbid medical illness poses many challenges when prescribing psychotropic drugs; important considerations include disease-induced changes in pharmacokinetics and pharmacodynamics while one must also consider drug-drug interactions and increased vulnerability to adverse effects.

Most drugs and substances that we ingest are metabolized by the liver. Impaired hepatic function can critically alter many aspects of pharmacokinetics. Knowledge of these processes and changes are essential to understanding changes in systemic drug concentrations and prescribing appropriately to avoid drug toxicity. Likewise, the use of psychotropic medications in gastrointestinal conditions is complicated by issues such as interaction between gastrointestinal medications and psychotropic drugs, risk of gastric bleed, and alteration in pharmacokinetics produced by conditions such as short bowel syndrome.

The present article will review the considerations when prescribing psychotropic drugs to patients with hepatic and gastrointestinal disorders. We summarize the pharmacokinetic changes and provide evidence-based dosing suggestions whenever available for individual agents of concern. The guideline first covers prescribing in hepatic disease, followed by gastrointestinal disorders.

2 Pharmacokinetic changes in hepatic disease

Hepatic impairment affects many critical aspects of pharmacokinetics (e.g., absorption, first-pass metabolism, hepatic biotransformation, the production of drug-binding proteins, and overall fluid status which determines the volume of drug distribution).[1] The reduced first-pass metabolism and hepatic biotransformation lead to an increase in oral bioavailability and prolonged drug effects. If serum albumin is reduced, then it will affect the highly protein-bound drugs.[2] In presence of ascites, the increased volume of distribution will affect the water-soluble drugs. **Figure 1** depicts the pharmacokinetic changes in liver disease.

There are two phases of drug metabolism in the liver; phase I reactions constitute hydrolysis, reduction, or oxidation and usually reduce the pharmacological activity of the molecule (except in cases where drugs are converted to their active metabolites). Phase II reactions involve drug conjugation with endogenous compounds such as glucuronic acid, amino acids, glutathione, and sulphate. This further reduces the pharmacological activity of the agent and makes it more water soluble.

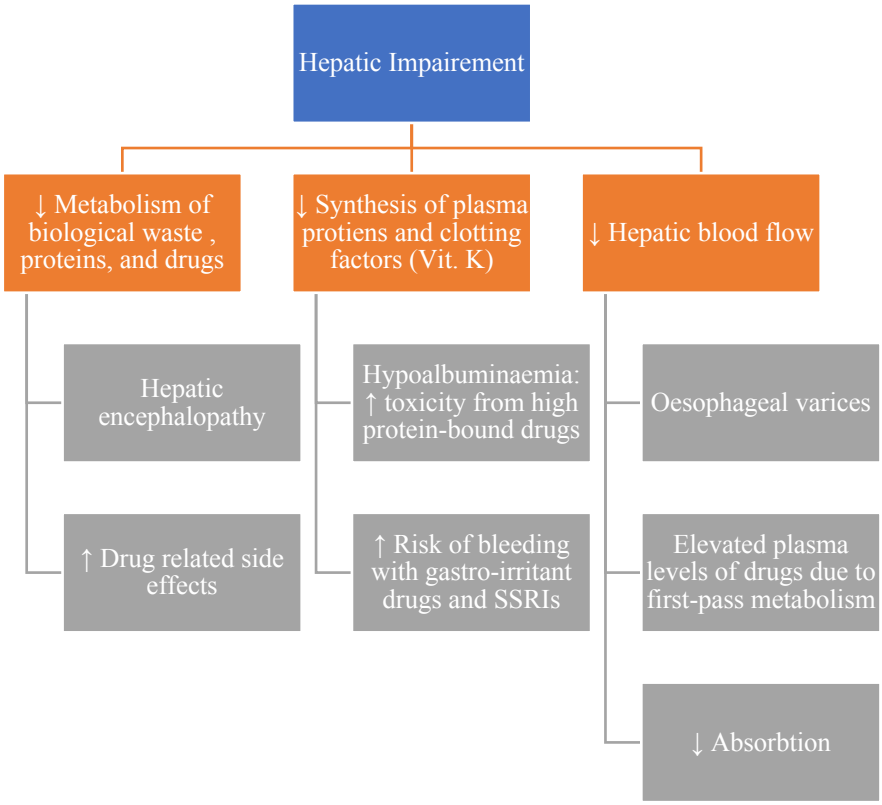
In chronic liver disease, more of the drug passes into the systemic circulation bypassing the liver; this is through the portosystemic shunts in these patients. Resultantly, there is a rise in drug levels which is more pronounced for drugs that undergo extensive first-pass metabolism. On the other hand, this is not seen for drugs that are mainly metabolized by phase II biotransformation reactions which are largely preserved in liver disease (such as lorazepam), and those with relatively little affinity for liver enzymes (such as paroxetine). Normally, phase II reactions are preserved in aging and liver disease. Hence, it is advisable to prefer

agents that do not need phase I reactions in end stage liver disease; examples of such agents are lorazepam and oxazepam.

Further, the free (unbound) fractions of drugs that are extensively protein bound undergoes a change because of decreased synthesis of albumin and glycoproteins in end stage liver disease. Many psychotropic drugs are highly protein bound; this includes tricyclic antidepressants, fluoxetine, sertraline, aripiprazole, and diazepam. A rise in serum levels of the free fractions of these agents may imply an increased risk of adverse drug reactions.

Most of the psychotropic agents that are currently used are lipophilic, implying that they need to be metabolized in the liver and made more soluble for them to get excreted in the urine or bile. Only a few drugs such as lithium and topiramate are hydrophilic, which are directly eliminated through the urine or bile.

Figure 1 – Pharmacokinetic changes in hepatic disease



3 Prescribing psychotropic drugs in hepatic disease

3.1 Depression

3.1.1 Mechanisms linking depression and chronic liver disease (CLD)

There are evidence to support a link between depression and chronic liver disease. Population based studies have shown high prevalence of depression in non-alcoholic fatty liver disease (NAFLD). Certain antiviral medications used to treat depression such as interferon (IFN) γ are "depressogenic." Indeed, studies on HCV-infected patients have shown that about 30-70% develop depression during IFN therapy. Finally, shared biological pathways such as

high levels of systemic inflammation and increased cortisol levels have also been postulated to underlie the links between NAFLD and depression.

3.1.2 Antidepressants in liver disease

3.1.3 Selective Serotonin Reuptake Inhibitors (SSRIs)

This class of antidepressants is generally believed to be safe for use in chronic liver disease. However, sertraline has been associated with fatal liver injury in uncontrolled observations. SSRIs with a lower risk of liver injury include fluoxetine, paroxetine, citalopram, and escitalopram. One concern when using SSRI in patients with liver disease is its association with gastrointestinal bleeding, and the extent of risk of bleeding in those with liver disease. Encouragingly, evidence from published reviews suggests that an increased risk of bleeding events with SSRIs in liver disease occurs only when co-prescribed with antiplatelet agents; this aligns well with recommendations in routine practice.

Typical pharmacokinetic changes seen in chronic liver disease prolongs the half-life and reduces drug elimination. The usual recommendation is to keep the maintenance dosage at 50% of that used for healthy individuals. However, no change is needed for the starting/initial doses.

There is evidence for efficacy of SSRIs in treating symptoms of depression in chronic hepatitis C infection. Paroxetine, dosed at 20 mg/day for four weeks, was found to be effective in reduction of depression scores among patients with IFN-induced depression. Similarly, in a randomized controlled trial comparing the efficacy of citalopram versus placebo in IFN-induced depression, citalopram dosed at 20 mg daily, separated from placebo at 2 and 4 weeks. Also, no major adverse effects were noted in therapeutic open label trials of SSRIs in hepatitis C patients. Dosing suggestions for major antidepressants in liver disease are shown in **Table 1**.

3.1.3.1 SSRIs and liver injury

Broadly, drug induced liver injury (DILI) can be classified into subtypes based on the pattern of liver injury or pathophysiological mechanism. Three main categories of liver injury have been described: hepatocellular, cholestatic, and mixed. These sub-types are distinguished based on the pattern of elevation of liver enzymes, i.e. *hepatocellular* injury is associated with elevated levels of serum alanine aminotransferase (ALT) with little to no increase in alkaline phosphatase levels (ALP), *cholestatic* liver injury shows a pattern of elevated serum ALP titres along with minimal elevation in ALT, whereas, in *mixed* liver injury both ALP and ALT titres are pathologically high.

Based on pathophysiology, liver injury can be divided into *idiosyncratic* (more common and dose-independent) or *intrinsic* type (dose-dependent and based on drug accumulation). Idiosyncratic liver injury can either be of the immune-mediated or allergic type, or metabolic type; the former is characterized by a hypersensitivity syndrome with symptoms of fever, eosinophilia and rash, and a short latency period for onset (1-6 weeks), the latter is characterized by a longer latency period (1 month to 1 year) and does not have a hypersensitivity reaction.

Challenges involved in assessing the potential for a psychotropic agent to induce liver injury are the lack of incidence studies, co-prescription of multiple psychotropic agents and

presence of medical co-morbidities (which make it difficult to ascertain causality), and the short duration and small numbers in the pre-marketing trials.

Table 1 – Dosing preferences for antidepressants in patients with chronic liver disease (CLD)[3]

Name of agent	Changes in metabolism in CLD	Prescribing suggestions
Selective Serotonin Reuptake Inhibitors (SSRI)		
Fluoxetine	Reduced clearance. Prolonged half-life. More time needed to attain steady state following dose adjustments.	Initiate at 5 mg or 10 mg daily. Titrate gradually. Not to exceed 40 mg daily in mild disease. Reduce dose or frequency by 50% in cirrhosis.
Fluvoxamine	Extensively metabolized by CYP2D6. Increased oral bioavailability and prolonged half-life expected.	Initiate at 25 mg daily. Titrate gradually. Not to exceed 100 mg daily in mild disease. Reduce dose or frequency by 50% in cirrhosis.
Paroxetine	Extensively metabolized by CYP2D6. Prolonged half-life and increased systemic exposure.	Initiate at 10 mg daily. Titrate gradually. Not to exceed 40 mg daily.
Sertraline	Extensively metabolized by CYP2D6. Prolonged half-life and increased systemic exposure.	Initiate at 25 mg daily. Titrate gradually. Not to exceed 100 mg daily.
Escitalopram	Extensively metabolized by CYP2C19 and CYP3A4. Reduced clearance (37%) and increased half-life.	Initiate at 5 mg daily. Titrate gradually. Not to exceed 10 mg daily.
Serotonin Noradrenaline Reuptake Inhibitors (SNRI)		
Venlafaxine	Extensively metabolized by CYP2D6. Oral bioavailability is increased 2-3 fold and half-life is prolonged.	Initiate at 37.5 mg to 75 mg daily. Titrate gradually. Not to exceed 150 mg daily. Avoid in decompensated liver disease or those at risk for seizures.
Duloxetine	Extensively metabolized. Reduced clearance (85%). Raised half-life and exposure.	Avoid in any degree of hepatic impairment.
Tricyclic Antidepressants (TCA)		
Amitriptyline	Extensively metabolized. Reduced clearance and increased half-life expected.	Reduce initial and maintenance dose to 50% with watchful escalation. Prefer second generation tricyclics (nortriptyline/desipramine) due to increased risk of sedation.
Imipramine	Extensively metabolized. Reduced clearance and increased half-life expected.	No dosing guidelines. Prefer second generation tricyclics (nortriptyline/desipramine) due to increased risk of sedation.
Noradrenaline reuptake inhibitor (NRI)		
Reboxetine	Raised half-life and exposure expected	Initiate at 50% of regular starting dose. Titrate cautiously.
Serotonin Antagonist and Reuptake Inhibitor (SARI)		
Trazodone	No data available	No dosing guidelines. Avoid in hepatic encephalopathy due to increased sedation.
Noradrenergic and specific serotonergic antidepressant (NaSSA)		
Mirtazapine	Reduction in clearance (33%). Raised half-life and exposure.	Initiate at 50% of regular starting dose. Titrate cautiously. Increased risk of serotonin syndrome when co-prescribed with other serotonergic agents.
Noradrenaline Dopamine reuptake inhibitor (NRI)		
Bupropion	Increase in half-life (70%) and systemic exposure in severe disease. No	In mild to moderate disease, do not exceed 75 mg daily (immediate release), 100 mg daily

	significant pharmacokinetic changes in mild to moderate disease.	(sustained release), or 150 mg every alternate day (extended release). Avoid in severe disease.

3.1.4 Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Venlafaxine and duloxetine have been associated with severe DILI in uncontrolled observations. Whereas venlafaxine has been associated with hepatocellular and cholestatic liver injury, all three types (hepatocellular, cholestatic, and mixed) of DILI have been noted with duloxetine. Both immunoallergic and metabolic mechanisms have been implicated for both these agents.

3.1.5 Tricyclic Antidepressants (TCAs)

These group of agents are well known for their anticholinergic side effects (dry mouth, constipation, urinary retention), orthostatic hypotension, arrhythmogenic effects, and central nervous system effects such as seizures and sedation. Clearance of these agents is generally reduced in patients with CLD. Hence, there may be an increased propensity for adverse effects at the regular dosage; for example, amitriptyline is shown to have increased sedating effects in a patient with cirrhosis of the liver. There is little data on the safety of other TCAs such as nortriptyline, imipramine, and clomipramine; on the other hand, there are few reports of DILI associated with some of these agents. Dosing suggestions in CLD can be found in **Table 1**. Caution must be exercised when prescribing TCAs to patients with hepatic encephalopathy due to increased risk of sedation and worsening of sensorium.

3.1.6 Monoamine Oxidase Inhibitors (MAOI)

Iproniazid, the first MAOI to be developed, was later withdrawn from the market during the late 70s due to reports of severe DILI even in apparently healthy patients. Most of these events occurred in the first 3 months of treatment, and mortality rates were high (up to 20%). Little data is available on the pharmacokinetics of other MAOIs in liver disease, though studies done on cirrhotic patients have shown prolonged half-lives and systemic clearance for tranylcypromine and moclobemide. While most authorities discourage the use of MAOIs in liver disease, if there is a need to use one, the reversible MAOI moclobemide may be preferred as compared to the irreversible MAOIs, as there is less risk for DILI.

3.1.7 Other antidepressants

The pharmacokinetics of agents such as bupropion and reboxetine are likely to be altered in patients with CLD. Particularly, bupropion has been associated with adverse effects such as nausea, vomiting, and seizures; as such, caution should be exercised when using it in patients with hepatic encephalopathy. On a similar note, trazodone is also associated with sedation and therefore, a similar caution is warranted. DILI with trazodone has been reported at normal therapeutic dosages.[4] Mirtazapine has also been associated with DILI related to prolonged jaundice, albeit rarely. Furthermore, there are reports of serotonin syndrome when mirtazapine is co-administered with other serotonergic drugs (i.e. SSRIs/SNRIs).

3.1.8 Use of antidepressants in liver transplant patients

Limited availability of controlled data on use of antidepressants among organ transplant recipients points to a lacuna in the literature that prevents drawing firm conclusions. Concerns about using antidepressants in this group center more on safety, adverse effects, and possible drug interactions with immunosuppressant agents than on potential differences in pharmacokinetic profiles seen in CLD patients.

Due to their favorable side effect profile, SSRIs and SNRIs are preferred over MAOIs and TCAs among liver transplant recipients. However, there are concerns about drug interactions; fluoxetine and paroxetine inhibit cytochrome P450 3A4 enzymes which are involved in metabolism of immunosuppressant medications such as cyclosporine and tacrolimus. Therefore, there may be a rise in systemic levels of these agents when co-administered with these SSRIs. Other SSRIs, namely escitalopram and sertraline, as well as SNRIs such as venlafaxine, exert only minor effects on cytochrome P450 enzymes which are unlikely to be clinically significant. However, given the mixed evidence on effects of SSRIs on serum levels of cyclosporine, a close monitoring of transplant recipients for tolerability issues is indicated. Interestingly, use of high dose corticosteroids has been linked to worse mental health outcomes in post-liver transplant recipients; hence, efforts must be made to minimize the use of corticosteroids among depressed graft recipients.

3.2 Anxiety

Higher rates of anxiety disorders have been found in patients with CLD.[5] Furthermore, presence of anxiety negatively correlate with health-related quality of life in this group. Common pathophysiology including metabolic (impairment in mitochondrial metabolism, inflammation, and oxidative stress), genetic (genes involved in lipid metabolism, inflammation, insulin signaling, and oxidative stress), lifestyle (unhealthy diet and lifestyle), and personality factors (low conscientiousness and high neuroticism) have been proposed to explain this association.[6]

As anxiety disorders are generally managed with agents that are also used for treating depression, readers may refer to preceding section for issues and considerations during the treatment. Dosing suggestions given in **Table 1** for antidepressants also apply for anxiety disorders in CLD. **Table 2** below presents dosing suggestions for other antianxiety agents, such as benzodiazepines, in hepatic insufficiency.

Table 2 – Dosage suggestions for anxiolytics in patients with chronic liver disease (CLD)[7,8]

Name of agent	Changes in metabolism in CLD	Prescribing recommendations
Benzodiazepines		
Alprazolam	Decreased metabolism and increased half life	Reduce dose by 50%. Avoid in severe liver disease
Chlordiazepoxide Diazepam Clonazepam Flurazepam	Extensively metabolized. Reduced clearance and increased half-life.	No adjustment needed for initial dose. Risk of drug accumulation and sedation accrues with time. Reduce maintenance dose by 50%. Avoid in patients with hepatic encephalopathy.
Lorazepam Oxazepam Temazepam	Metabolized via conjugation. Clearance is not affected.	To be preferred in CLD. No specific dose adjustment needed. Escalate dose gradually due to prolonged onset of action. Avoid in patients with hepatic encephalopathy.
Other anxiolytics		
Buspirone	Extensively metabolized. Half-life expected to be increased.	Reduce dosage and frequency by 50% in mild to moderate impairment. Avoid in severe disease.
Ramelteon	Extensively metabolized. Raised systemic levels in mild and	Reduce dose in mild to moderate impairment. Avoid in severe disease

	severe disease.	
Zaleplon Zolpidem	Metabolized in liver. Reduced clearance and prolonged half-life.	Start with 2.5 mg dose of immediate release preparation. Recommended ceiling dose is 5 mg. Avoid in severe disease as it may precipitate hepatic encephalopathy.
Eszopiclone Zopiclone	Metabolized in liver	No dose adjustment necessary for mild to moderate disease. Reduce dose by 50% in severe disease.

3.3 Psychotic Disorders

Among patients with chronic liver disease due to hepatitis A, Wilson's disease, or chronic liver disease due to non-hepatocellular causes such as extensive portosystemic collateral circulation, schizophrenia is not an uncommon occurrence. Several reasons may be proposed to explain this association; first, drugs used to treat schizophrenia such as antipsychotics may cause liver injury and dysfunction. Schizophrenia may be associated with unhealthy lifestyle practices including substance use, that itself increases the risk of medical co-morbidity and liver disease.[9] Finally, common biological and biochemical perturbations such as increased central and systemic levels of certain biogenic amines and decreased levels of gamma amino butyric acid (GABA) seen in both conditions may explain this association.[10]

3.4 First generation antipsychotics

Neuroleptics have been frequently associated with development of steatosis. Phenothiazines (e.g. chlorpromazine) and butyrophenones (e.g. haloperidol) have been associated with elevated liver enzymes, and rarely, hepatocellular failure; in both cases, the type of lesion is cholestatic and related to immuno-allergic mechanisms. Of the two agents, phenothiazines have been more frequently implicated in liver damage compared to butyrophenones. Large case series of severe DILI associated with use of first generation antipsychotics (FGAs) have been published.[11,12]

3.5 Second generation antipsychotics

These group of agents are, in general, safer compared to FGAs in liver disease. Nevertheless, usage of second-generation antipsychotics (SGA) may lead to metabolic syndrome and this, in turn, can lead to non-alcoholic fatty liver disease. Asymptomatic elevation in hepatic transaminases and bilirubin may also occur when using these agents. Hence, it is good practice to obtain baseline liver function tests before initiating SGAs, and subsequently monitor at regular intervals (every year). In patients who are on clozapine as well as those who are regular users of alcohol or other substances, more frequent monitoring may be warranted.

As a rule, it is recommended to stop antipsychotics if there is a symptomatic elevation of hepatic transaminases or asymptomatic elevation of more than 3 times the normal upper limit of liver enzymes. Extra caution should be exercised among patients with pre-existing liver disease or those who are concurrently receiving potentially hepatotoxic medications. Because these agents are relatively new, there is a paucity of controlled data on prevalence and risk factors for DILI associated with SGAs. In a review of 10 group studies and 91 case reports/series, Marwick and colleagues found a median of 32% for any abnormal liver function test while the median for clinically significant liver enzyme elevation was 4%.[13] Most such reactions were asymptomatic, arose in the first 6 weeks, and were self-limiting.

The most common antipsychotic associated with acute liver injury was chlorpromazine. **Table 3** shows the changes in metabolism and prescribing suggestions for commonly used antipsychotics in liver disease.

Table 3 – Prescribing suggestions for anti-psychotics in patients with chronic liver disease (CLD)[7]

Name of agent	Changes in metabolism in CLD	Prescribing suggestions
First generation antipsychotics (FGA)		
Haloperidol	Extensively metabolized by liver via CYP3A4 but consistent alteration in kinetics not identified.	No specific recommendations but reduce dose and titrate slower than usual. Avoid in those who are actively using alcohol
Chlorpromazine	Undergoes extensive first pass metabolism in liver. Can cause acute cholestatic liver injury.	Avoid all phenothiazines in liver disease. Prefer non-phenothiazine FGAs if necessary.
Second generation antipsychotics (SGA)		
Aripiprazole	Extensively metabolized. Half-life and plasma concentrations are expected to be increased.	No dosage adjustments recommended by manufacturer in mild to severe liver injury.
Clozapine	Extensively metabolized. Highly protein bound. Elevated systemic exposure expected.	No dosing guidelines. Discontinue if hepatic transaminases are markedly elevated. Avoid in patients with clinical signs such as jaundice.
Olanzapine	Extensively metabolized by liver. Half-life may be increased in CLD.	In severe liver disease, start at 5 mg daily and escalate slowly as per response. Periodic assessment of transaminases needed.
Risperidone	Undergoes hepatic biotransformation. Free fraction of drug is raised by 35% in severe disease.	Start at 0.5 mg once or twice daily and escalate dose in increments of maximum 0.5 mg twice daily. Increases beyond this limit should be done at intervals of ≥1 week.
Quetiapine	Extensively metabolized by liver. Half-life may be increased in CLD.	In severe liver disease, start immediate release preparations at 25 mg daily and escalate slowly (25-50 mg increments) as per response. Periodic monitoring of transaminases needed.
Ziprasidone	Extensively metabolized by liver. Half-life may be increased in CLD.	No dosage adjustments recommended by the manufacturer.
Paliperidone	Renally excreted	Safe. No dosage adjustments needed in mild to moderate liver disease. No dosing guidelines in severe disease.

3.6 Bipolar Disorders

Evidence from population-based studies suggest that patients with bipolar disorder have an increased prevalence and incidence of liver disease compared to population controls; the risk is increased among males, concurrent use of SGAs or antidepressants, and those with hyperlipidemia.[14] Current and lifetime prevalence of hepatic illness in bipolar disorder were 17% and 21%, respectively.[15] Increased incidence of medical co-morbidities in bipolar disorder (which increases the risk of NAFLD), unhealthy lifestyle factors including alcohol

and other substance use, and common underlying pathological mechanisms (such as raised systemic inflammation) are factors that may explain this association.

Among the mood stabilizing agents that are used to control symptoms of bipolar disorder, lithium is minimally metabolized in the liver and not protein bound. It is generally believed that lithium is safe to use in hepatic dysfunction. However, a few things must be kept in mind when using lithium in patients with CLD. First, people with liver dysfunction can also have renal impairment which leads to precarious fluid balance. Given this scenario, maintaining therapeutic serum levels of lithium becomes challenging. It is important to closely monitor serum lithium levels in such a scenario. Second, long term lithium therapy has been associated with deranged liver function tests. Though most of these changes are reversible with time and do not necessitate change of drug, episodes of lithium toxicity can cause more marked changes in liver function tests.

Commonly used antiepileptic mood stabilizing agents are valproate, carbamazepine, topiramate, gabapentin, and lamotrigine. Of these, valproate and carbamazepine are associated with maximum risk of hepatotoxicity, while gabapentin is considered safe as it is minimally metabolized by the liver,[16] though there are case reports of gabapentin-induced hepatotoxicity.[17]

Asymptomatic elevations in hepatic transaminases can be seen in 10 to 15% of patients on valproate, while hyperbilirubinemia can be seen in up to 44% cases. As long as these elevations are within three times the upper limit of normal range, valproate may be continued. Valproate-induced liver injury is more common among infants and children and is an idiosyncratic metabolic phenomenon.[18] Valproate-induced hyperammonemic encephalopathy is a serious adverse reaction that can result uncommonly from acute DILI due to valproate and consequently raised liver enzymes,[19] though the more common cause is inhibited activity of key enzymes involved in urea cycle such as carbamoyl phosphate synthetase-1 and ornithine transcarbamylase.[20] Concurrent use of topiramate and other antiepileptics is a risk factor for hyperammonemia due to valproate.

About 10% of patients initiated on carbamazepine experience hypersensitivity reactions, of which ~10% report hepatic adverse events leading to a 1% incidence rate of carbamazepine-induced DILI. Common symptoms of carbamazepine-induced hypersensitivity and liver damage are fever, skin rash, facial edema, enlarged lymph nodes, and leukocytosis, which typically begin 1-8 weeks after initiation of the drug.[21] Lamotrigine and topiramate are infrequently associated with liver enzyme elevation and idiosyncratic hepatotoxicity. Prescribing suggestions for common mood stabilizers in liver disease are shown in **Table 4**.

Table 4 – Prescribing suggestions for mood stabilizers in patients with chronic liver disease (CLD)[7,22]

Name of agent	Changes in metabolism in CLD	Prescribing suggestions
Lithium	Renally excreted. No appreciable hepatic metabolism	Not metabolized in liver. Renally excreted. Dose must be adjusted based on fluid balance.
Valproate	Highly protein bound. Hepatic biotransformation, the main route of elimination is affected. Reduced clearance and increased half-life	Reduce dosage. Monitor LFT frequently (particularly in first 6 months of treatment). Avoid in patients with severe hepatic dysfunction.
Carbamazepine	Hepatic biotransformation is the main route of elimination	No dosing guidelines but prudent to reduce dose and monitor LFTs. Discontinue if aggravation of liver function ensues.
Oxcarbazepine	Undergoes hepatic biotransformation but liver disease does not affect kinetics of either the parent drug or active metabolite	No dosage adjustment required for mild to moderate liver disease, as per manufacturer
Topiramate	Reduced clearance.	Mainly excreted unmetabolized by kidneys. In moderate to severe liver disease, doses to be reduced by 30%, as per product monograph.
Lamotrigine	Undergoes hepatic metabolism. Reduced clearance	Starting, up titration, and maintenance dosages should be reduced by 50% in moderate liver disease (Child-Pugh B) and by 75% in severe liver disease (Child-Pugh C)
Gabapentin	Renally excreted. No appreciable hepatic metabolism.	No dose adjustment needed.

LFT=Liver Function Tests

3.7 Substance Use Disorders

Substance use, in particular chronic use of alcohol, is an important cause of liver disease. Many such patients may present with alcohol withdrawal of varying severity ranging from simple withdrawal to severe cases with seizures and delirium tremens. Benzodiazepines are the drugs of choice in management of alcohol withdrawal as they reduce the risk of withdrawal-related seizures and delirium tremens.

Among the benzodiazepines, lorazepam or oxazepam are preferred for detoxification in alcohol withdrawal as they only undergo glucuronidation (phase II metabolism) in the liver and do not require to undergo phase I biotransformation. As discussed in section 1, phase II reactions are largely preserved in liver disease. Following detoxification, among pharmacological agents used to promote abstinence and prevent relapse in alcohol use disorders, naltrexone and acamprosate have more evidence for efficacy than disulfiram.[23] Naltrexone has an FDA “black box” warning against use in patients with liver disease; therefore, it must be avoided in such cases. Although there is a dearth of controlled trials investigating the safety of acamprosate in alcoholic liver disease, considering that it does not undergo hepatic metabolism and there are few reports of DILI associated with acamprosate, it may be preferred option for pharmacoprophylaxis in alcoholic liver disease. Dosing in liver disease and safety considerations for commonly used medications in alcohol use disorders are shown in **Table 5**.

Another category of substances with significant implications in liver disease is opioids. Most opioids are, at least to some extent, metabolized by the liver. Liver failure due to hepatitis C is one of the leading indications for liver transplant. The prevalence of hepatitis C among drug users on methadone maintenance therapy ranges from 84 to 90%.[24,25] Hence, it is important to know dosing considerations when using pharmacologic treatments for opioid dependence. Studies of methadone maintenance treatment have not found evidence for long term damage to liver.[26] However, liver disease may be a risk factor for methadone overdose, as methadone clearance is impaired in chronic liver disease.[27]

Buprenorphine is metabolized by the cytochrome P450 3A4 enzyme system in the liver but investigators who looked at interactions with HIV medications that inhibit this cytochrome enzyme did not find evidence for clinically significant drug interactions, except when buprenorphine was co-administered with atazanavir or ritonavir.[28,29] As mentioned earlier, naltrexone, an FDA approved agent for use in opioid dependence, has a potential to impair liver function tests and must be avoided in patients with preexisting liver disease.

3.8 Management pearls

When initiating opioids for pain relief in liver disease patients, always initiate lower doses with longer interval between doses, and assess ability of patients to tolerate before administering higher dosages. Hydromorphone and fentanyl are preferred agents for pain relief in cirrhotic patients as they are least affected by ongoing hemodynamic disturbance.[30] Close monitoring is warranted and those who are showing signs of deteriorating liver function should be assessed for symptoms of opioid toxicity, and necessary dose reduction should be undertaken. Because all opioids are metabolized in the liver, at least partially, the potential for concurrently administered non-opioid medications to affect the metabolism of opioids by inducing or inhibiting the CYP family of enzymes must be borne in mind. Finally, because most patients with liver disease also have an increased likelihood of renal dysfunction (i.e. hepatorenal syndrome), and because renal impairment can impact opioid levels and elevate risk of toxicity, dose adjustments based on glomerular filtration rate may be a prudent approach.[31]

Table 5 – Medications for alcohol use disorder (AUD) and their safety in alcoholic liver disease (ALD)[32]

Name of agent	Pharmacologic target	Dosage	Safe/not in ALD
FDA approved medications for AUD			
Naltrexone	Mu opioid receptor antagonist	50 mg daily orally or 380 mg monthly intramuscular injection	No (use with caution in alcoholic liver disease)
Acamprosate	NMDA receptor agonist	666 mg thrice daily or 333 mg thrice daily depending on body weight	Yes (except for severe chronic liver disease)
Disulfiram	Inhibits aldehyde dehyrogenase	250-500 mg daily orally	No
Non-FDA approved medications for AUD			
Baclofen	GABA-B receptor agonist	30-40 mg once daily (up to 80 mg)	Yes (except for severe chronic liver disease)
Gabapentin	Modulates GABA synthesis; α2δ-1 ligand	900-1800 mg in two or three divided doses daily	Yes
Topiramate	Affects multiple	300 mg once daily (once daily	Yes (but use with caution in

	systems (GABA/Glutamate)	formulation) or in two divided doses (regular formulation)	hepatic encephalopathy as side effects like cognitive impairment may confound management)
Ondansetron	5HT3 Antagonist	1-16 µg/kg twice daily	Yes (but some inconclusive case reports of liver toxicity exist)
Varenicline	Nicotinic acetylcholine receptor partial agonist	1 mg twice daily orally (lower starting dose)	Yes

NMDA=N-methyl D-aspartate; GABA=Gamma Amino Butyric Acid; FDA=Food and Drug Administration (USA)

3.9 Managing cognitive impairment and attention-deficit hyperactivity disorder in hepatic insufficiency

Neurocognitive dysfunction has been noted in a range of liver diseases (chronic hepatitis C, Wilson's disease, alcoholic liver disease, and primary biliary cirrhosis). Moreover, such impairment is associated with significant negative impact on activities of daily living and quality of life. Certain drugs used to treat attention-deficit hyperactivity disorder (ADHD) are associated with severe drug induced liver injury.[33] While prescribing in such situations, the clinician must be cognizant of the balance between risk of serious adverse effects and clinical efficacy as well as the dosage adjustments necessary based on the severity of hepatic insufficiency. **Table 6** below summarizes prescribing suggestions for key procognitive agents and psychostimulants in hepatic insufficiency.

Table 6 – Prescribing suggestions for cholinesterase inhibitors, memantine, and psychostimulants in patients with chronic liver disease (CLD)[7]

Name of agent	Changes in metabolism in CLD	Prescribing suggestions
Procognitive agents		
Donepezil	Mildly reduced clearance	No specific dosing suggestions
Galantamine	Extensively metabolized by liver. Clearance reduced.	Use with caution in mild to moderate dysfunction (doses not to exceed 16mg/day). Avoid in patients with severe hepatic dysfunction.
Rivastigmine	Major route of clearance is renal. Minimal hepatic metabolism.	Dose adjustment may not be necessary.
Memantine	Primarily eliminated by the kidney.	No dosage adjustment required as per manufacturer
Psychostimulants		
Methylphenidate	Minimal data in patients with hepatic impairment. Reports of hepatotoxicity, most likely idiosyncratic exist.	No dosing guidelines are available. Use with caution.
Atomoxetine	Undergoes extensive hepatic metabolism. Reduced clearance.	Initial and target dose must be reduced by 50% in moderate impairment (Child-Pugh B) and by 75% in severe liver dysfunction (Child-Pugh C)
Modafinil, Armodafinil	Reduced clearance.	In severe hepatic impairment reduce dose by 50%

3.10 Management of Neuropsychiatric effects of Interferon-Alpha in Hepatitis C

Chronic Hepatitis C virus infection is a leading cause of liver transplantation worldwide. IFN-α is commonly used for the treatment of hepatitis C infection, but is associated with a range of significant neuropsychiatric side effects. These include cognitive impairment, mood changes (commonly depression, but mania may also occur), neurovegetative symptoms (fatigue, malaise, and lethargy), suicide ideation, and rarely, delirium or psychosis. Depression is the most common neuropsychiatric adverse effect with IFN-α; up to 10-50% of patients on therapy with IFN may develop depression.

Psychotropic medications that have a known association with blood dyscrasia, such as carbamazepine, clozapine, mirtazapine, and valproate must be avoided in patients with hepatitis C who are on IFN therapy because hematological abnormalities are common in this population. Antidepressants with prominent anticholinergic effect (such as tricyclic agents) must be avoided too, as they can further worsen cognitive impairment in these patients. SSRIs are the drugs of choice in IFN-induced depression in hepatitis C, and are in general well tolerated, though concerns have been raised about the risk of gastric bleed. These agents have evidence for efficacy in both acute phase and prophylactic management aimed at reducing the frequency and intensity of IFN-induced depression.[34,35]

4 Hepatic monitoring preferences when initiating psychotropic agents

It is not necessary to measure hepatic functions before starting all psychotropic medication. Some psychotropic medications may require dosage adjustment in those with hepatic disease, for which baseline hepatic function measurement is essential. In the absence of any prior studies, a baseline liver function test is considered useful. However, the treatment can be initiated in urgent situations if there is no clinical evidence of hepatic disease.

Also, few of the psychotropic drugs are hepatotoxic (**Table 7**), that require monitoring at periodic intervals (e.g. valproate, carbamazepine, and disulfiram). For other drugs, liver function tests should be checked if there are clinical symptoms of hepatic disease such as fatigue, right upper quadrant abdominal pain, jaundice etc. The most common type of hepatotoxicity seen in more than 90% is elevated serum ALT levels, with little change in ALP levels. Sometimes, a cholestatic pattern is seen with high ALP levels with slightly raised ALT levels. High serum bilirubin along with these changes suggests severe hepatocellular damage and poorer prognosis. Occasionally steatosis or steatohepatitis is seen with psychotropic drugs, which is usually reversible.

Table 7: Hepatotoxic psychotropic drugs and preferred monitoring frequency[18,36,37]

Drug	Hepatotoxicity	Monitoring
Valproate	Transaminitis (10-15%), Hepatitis, Fulminant hepatic failure, Hyperammonemia	Baseline, every 3 to 6 months
Carbamazepine	Transaminitis (61%), Hepatitis (1%)	Baseline, every 3 to 6 months
Chlorpromazine	Transaminitis (25-50%), Cholestatic jaundice (0.1-1%)	Baseline, every 3 to 6 months
Haloperidol	Transaminitis, cholestasis	Baseline, every 3 to 6 months

Olanzapine, Risperidone, Quetiapine	Transaminitis, cholestasis, steatohepatitis	Baseline, every 3 to 6 months
Clozapine	Transaminitis (37%), fulminant hepatic failure, hepatitis	Baseline, every 3 to 6 months
MAOI	Hepatocellular injury	Baseline, every 3 to 6 months
TCAs	Transaminitis, Cholestatic or Hepatocellular injury	Baseline, every 3 to 6 months
SSRI/SNRI	Acute hepatitis, Steatohepatitis, Transaminitis	Baseline, every 3 to 6 months
Disulfiram[38]	Acute hepatitis, Fulminant hepatitis	Baseline, 2-week intervals for 2 months, 3 to 6-month intervals thereafter.

MAO=Monoamine Oxidase Inhibitors; TCA=Tricyclic Antidepressants; SSRI= Serotonin Reuptake Inhibitors; SNRI=Serotonin Norepinephrine Reuptake Inhibitors

If liver function tests show mild transaminase elevations, the drug can be continued with regular monitoring at more frequent intervals. Transaminase levels of three to four times of the upper value (i.e. 120 to 160) is an indication to discontinue the offending drug. If it is clinically indicated to continue the drug, a dose reduction may be attempted, however, there is no evidence that such strategy is helpful. If there is a history of such hepatic inflammation with a drug, it is likely to appear with rechallenge, hence better avoided if an alternative treatment option is available.

Valproate therapy is associated with hyperammonemia, specifically in those with other risk factors such as lower carnitine levels. It is not mandatory to routinely check serum ammonia levels before initiating treatment on valproate. If a patient develops clinical signs associated with hyperammonemia such as drowsiness, lethargy, altered mental status, serum ammonia levels may be monitored and valproate should be stopped. Sometimes, levocarnitine can be given for resolution of the hyperammonemia. Dose reduction of valproate may help in some patients. The differential diagnosis of valproate-induced non-hepatic hyperammonemic encephalopathy (VNHE) include other reasons such as urea cycle disorders (late onset ornithine transcarbamylase deficiency), or organic acidemias such as methylmalonic acidemia, proprionic acidemia, and multiple carboxylase deficiency. Risk factors for VNHE include those for secondary carnitine deficiency such as malnutrition, chronic renal failure, ketogenic diet, strict vegetarianism, and concurrent treatment with certain antiepileptics that can lower carnitine levels (e.g. topiramate, phenytoin, carbamazepine, and phenobarbitone).

5 Drugs that escape hepatic metabolism

Most of the psychotropic drugs are extensively metabolized by liver. There are some drugs that escape hepatic metabolism, a knowledge of which will be helpful for clinical considerations in those with hepatic diseases.[39] Some of the drugs are not metabolized at all by liver, and are predominantly excreted through kidneys (**Table 8**). Some other drugs are only minimally metabolized by liver, i.e. there are no phase 1 oxidation reactions that occur through cytochrome P450 system, but only phase 2 conjugation reactions which are relatively preserved in hepatic cirrhosis (**Table 9**). Also, the proportion of drug that is metabolized by the liver in contrast to the proportion that is excreted unchanged is relevant while deciding on the psychotropic and their dose (e.g. paliperidone and milnacipran).

It is known that those with cirrhosis have lower glomerular filtration rates, and lower creatinine levels because of reduced hepatic synthesis of creatine. Therefore, in patients with cirrhosis, medications with predominantly renal elimination and with narrow therapeutic index, such as lithium, should be used with caution. Also, serum creatinine levels are not good measure of glomerular filtration rates in those with cirrhosis and tend to overestimate it. Similarly, acamprosate is not metabolized by liver and is considered safe in liver disease. However, safety of acamprosate is not established in those with Child-Pugh class C cirrhosis. Some medications do not require any dose adjustments in cirrhosis (e.g. gabapentin and pregabalin), and should be the preferred drugs if clinically indicated.

Drugs that are only minimally metabolized and undergo only conjugation reactions are considered relatively safe and are preferred over those that involves cytochrome P450 metabolism (e.g. lorazepam over diazepam for alcohol withdrawal in alcoholic liver disease). However, it is known that conjugation reactions are also impaired in advanced liver disease such as cirrhosis. Therefore, in patients with cirrhosis it is prudent to make appropriate dose adjustments. A usual strategy is 50% of the usual dose in a Child-Pugh class A patient, and 25% in Child-Pugh class B patients, along with monitoring for signs of toxicity.[40] For those with Child-Pugh class C patients, these medications are to be preferred only if clinical safety data is available.

Table 8 - Drugs not metabolized by liver

Drugs	Elimination	Comments
Lithium[41]	Not metabolized, eliminated through kidneys mostly, and small amount through saliva, sweat, feces.	Dose adjustments required in cirrhosis. Serum creatinine is not a good measure of glomerular filtration rate in cirrhosis.
Acamprosate[42]	Half of acamprosate is eliminated as unchanged acetyl-homotaurine in urine, the other half by biliary excretion.	The pharmacokinetics of acamprosate is not modified in patients with hepatic insufficiency (Child-Pugh class A or B). Not studied in Child-Pugh class C, hence, contraindicated.
Gabapentin, pregabalin[43]	Not metabolized, excreted unchanged in urine and feces	No dose adjustment required in liver disease

Table 9 - Drugs that are minimally metabolized by liver

Drugs	Elimination	Comments
Lorazepam, Oxazepam	Conjugation reaction only, elimination of conjugated products through kidneys	Can be used in Child-Pugh class A or B with dose adjustments (50% or 25% of usual dose)
Lamotrigine[43]	2-N and 5-N glucuronidation, excreted through kidneys	Reduce dose by up to 50% in Child-Pugh class B or C without ascites, and by 75% in Child-Pugh class C with ascites
Topiramate[43,44]	Only 20% drug is metabolized (hydroxylation and hydrolysis, glucuronidation), 80% excreted unchanged in urine	Dose reduction required by 30% in severe liver disease
Levetiracetam[43]	Only 24% is hydrolyzed and 2% metabolized, 66% is excreted unchanged in urine	No dose adjustment in mild to moderate liver disease, reduce dose by 50% in Child-Pugh class C

Paliperidone[45,46]	Limited hepatic metabolism, 60% eliminated unchanged in urine and 11% in the faeces	No dose adjustment in mild to moderate liver disease
Amisulpride[45,47]	20-25% drug is eliminated unchanged in urine, minimal metabolism (oxidation, N-deethylation, and hydroxylation)	Relatively safe in mild hepatic disease
Milnacipran[48,49]	50-60% drug is eliminated unchanged in urine, 20% as glucuronide, rest through dealkylation and hydroxylation followed by glucuronidation	No dosage adjustment is needed in liver disease (Child-Pugh class A, B or C)

6 Prescribing in gastrointestinal disease

Psychological stress and illness are prevalent among patients with gastrointestinal (GI) disease. Psychological distress may be the cause of, exacerbate, or be a result of these disorders. Therefore, psychotropic medications are frequently required for the treatment of GI disorder symptoms and comorbid psychopathology. Prescription of psychotropic medications in these patients is frequently difficult due to potential interactions between GI medications and psychotropic agents, risks of prescription, and alterations in drug pharmacokinetics due to underlying GI disorders (e.g., hepatic failure, short bowel syndrome).

6.1 Gastric bleeding

SSRIs may prolong upper GI bleeding in patients receiving non-steroidal anti-inflammatory drugs, thrombocytopenic, or has other platelet dysfunction (e.g., von Willebrand disease).[50] SSRIs do not appear to increase the risk of GI bleeding in patients receiving warfarin, but they may increase the risk for non-GI bleeding.

6.2 Over-the-counter (OTC) antacids

Interactions between over-the-counter (OTC) GI medications and psychotropic medications can affect drug absorption. Antacids and sucralfate reduce drug absorption by increasing the gastric pH and delaying gastric emptying. In such scenario, it is advised that antacids should be taken at least 2 -3 hours apart from other drugs. Furthermore, the antacid may increase the renal excretion of lithium by increasing sodium excretion.[51]

Histamine receptor antagonist (e.g., cimetidine) inhibits the oxidative metabolism of most drugs including psychotropic medication. Therefore, reduction of psychotropic medications or avoidance of histamine receptor antagonists (e.g., cimetidine) is recommended.[51] Some proton pump inhibitors (e,g, esomeprazole, lansoprazole) induces the CYP 1A2,which increases the elimination of clozapine and olanzapine. On other hand, some proton pump inhibitors (such as omeprazole) inhibit CYP 2C19 and thus increases the level and toxicity of diazepam, flunitrazepam, and phenytoin.[51]

6.3 OTC antiemetics

Concurrent use of 5-HT3 antagonists (e.g. ondansetron) along with TCAs, typical/atypical antipsychotics, and lithium may increase the risk of cardiac arrhythmias and QT prolongation.[2,51] Dimenhydrinate, diphenhydramine, and promethazine increase the risk of cognitive impairment and delirium in combination with psychotropic drugs with prominent

anticholinergic effect. In addition, these medications may reduce the therapeutic effect of cholinesterase inhibitors and memantine.[2,51]

Domperidone and droperidol can cause extrapyramidal symptoms when combined with antipsychotics. In addition, these medications may increase the risk of cardiac arrhythmias and QT prolongation when combined with other psychotropic drugs (such as TCAs, typical/atypical antipsychotics, and lithium).[2,51] The use of metoclopramide in combination with antipsychotics can cause extrapyramidal symptoms[2,51]. Glucocorticoids induce CYP 3A4 enzyme, which ultimately leads to increased metabolism and reduced level of oxidatively metabolized drugs (e.g., benzodiazepine, carbamazepine, quetiapine).[2,51]

Dronabinol can produce additive sympathomimetic effects such as additive hypertension, tachycardia, and possible cardiotoxicity (with amphetamines, methylphenidate, and other sympathomimetics), additive hypertension, tachycardia, and drowsiness (with TCAs), and additive drowsiness and CNS depression (with benzodiazepines, lithium, opioids, and buspirone).[2,51]

6.4 OTC anticholinergics/antispasmodics

Antispasmodics (e.g., dicyclomine, glycopyrrolate) increases the risk of cognitive impairment and delirium in combination with psychotropic drugs with anticholinergic effect. In addition, these medications may reduce the therapeutic effect of cholinesterase inhibitors and memantine.

6.5 Gut microbiota and effect on psychotropic drugs

A growing body of research supports the role of the gut microbiome in modifying the action of therapeutic drugs. Likewise, the relationship between psychiatric disorders and gut microbiota has been a major research focus in recent times. Specifically, alterations in gut microbial compositions have been reported in a range of psychiatric disorders including depression, bipolar disorder, schizophrenia, ADHD, and autism spectrum disorders. The interaction between gut microbiota and psychotropic drugs is bidirectional: effect of gut microbiota on the pharmacokinetics and pharmacodynamics of psychotropic agents, and impact of psychotropic agents on gut microbiota compositions.[52]

Preclinical studies have shown that depletion in gut microbiota, following use of antibiotics or probiotics, lead to an increase in bioavailability of olanzapine, but exerted no appreciable effects on bioavailability of risperidone.[53] This suggests that the effect of gut microbiome depletion may be drug specific. On a similar note, antibiotic induced depletion of gut microbiome attenuated olanzapine-related metabolic changes among rats.[54] In fact, a recent meta-analysis,[55] that examined both human and animal studies, concluded that antipsychotic-induced alterations in gut microbiome may underlie drug-induced weight gain and metabolic disturbance noted during treatment.

The other key aspect in the relationship is changes in gut microbiome composition induced by psychotropic usage. Certain FGAs (e.g. thioridazine, fluphenazine, and chlorpromazine) have been shown to have antimicrobial properties in vitro. Cross-sectional studies on humans have shown significant differences between microbiota communities between antipsychotic treated and drug free people with bipolar disorder. Furthermore, evidence from in vitro and in vivo studies suggest that a range of antidepressants including TCA, SSRI, and ketamine may exert antimicrobial effect against different bacterial strains, though whether these effects

mediate drug response and toxicity remain unclear. The implications of these findings are many and pertain to issues with drug selection, drug safety, and efficacy. In future, microbiome measures may be integrated into clinical practice to assess these issues and inform patient management.

6.6 Irritable Bowel Syndrome (IBS) and other Functional Gastrointestinal Disorders (FGIDs)

Psychotropic medications can be used to treat irritable bowel syndrome (IBS), other FGIDs, and associated psychiatric comorbidities. It is necessary to consider potential interactions between gastrointestinal and psychotropic medications and risks involved in prescribing psychotropic agents in various FGIDs. **Table 10** summarizes specific prescribing suggestions that can be used in conjunction with the standard treatment.

Table 10 - Prescribing suggestions in patients with irritable bowel syndrome (IBS) and other Functional Gastrointestinal Disorders (FGIDs)

Medical Conditions	Preferred psychotropic medication
IBS	**IBS with diarrhea and abdominal spasms** *:* TCAs (Desipramine, imipramine, and amitriptyline)[51]
	Constipation-predominant IBS : SSRIs (Fluoxetine, Citalopram and Paroxetine).[51] Oral guanylate cyclase C agonists (linaclotide for constipation in IBS, plecanatide for chronic idiopathic constipation) can be used if available. TCAs should be avoided in constipation-predominant IBS.
Fecal Incontinence	A low dose of anticholinergic medications (e.g., amitriptyline 20 mg/day)[56]
Functional Diarrhea	Loperamide, desipramine (25-200 mg/day)[2,51]
Constipation	Behavioral interventions (such as increased fiber in the diet, fluid intake, physical activity, bulking agents), osmotic laxatives and stool softeners (e.g., polyethylene glycol).
Burning Mouth Syndrome	Topical clonazepam (1 mg clonazepam tablet for 3 minutes and then spit): Most effective agent Other drugs: sertraline 50 mg/day, amisulpride 50 mg/day, and paroxetine 20 mg/day
Xerostomia	Cholinergic agents [pilocarpine (1% solution diluted from eye drops) or bethanechol (5–10 mg sublingually)][51,57]
Dysphagia	**Acute dystonia**: Intravenous diphenhydramine or benztropine **Dysphagia caused by drug-induced parkinsonism or Tardive dyskinesia** : lower antipsychotic doses, switching agents, or discontinuation of therapy[51]
Globus hystericus	TCAs and MAOs in conjunction with reassurance and education[51]
Gastroesophageal Reflux Disease	Antidepressants (TCAs, SNRIs) and benzodiazepines [Diazepam (ranging from 5 mg twice daily to 10 mg three times daily)] Avoid : Low-potency antipsychotics and tertiary amine TCAs[2,51]
Peptic Ulcer Disease	TCAs may be useful in the treatment and prevention of duodenal ulcers [2,51]
Gastroparesis	SSRIs, phenothiazines, benzodiazepines, and mirtazapine. Avoid psychiatric drugs with anticholinergic actions and metoclopramide[2,51]
Cyclic vomiting syndrome	Prokinetics, antiemetics, erythromycin, sumatriptan, TCAs, benzodiazepines, and anticonvulsants (valproate, topiramate, zonisamide, levetiracetam) [51].
Hyperemesis gravidarum	Psychotropic medications (e.g., olanzapine, chlorpromazine mirtazapine) may help to reduce symptoms[2,51]
Cancer related nausea and vomiting	Antipsychotics (e.g., olanzapine, chlorpromazine), antidepressants (e.g., mirtazapine), 5-HT3 receptor antagonists, neurokinin receptor antagonists,

	anticholinergics, antihistamines, cannabinoids, and benzodiazepines[2,51]
Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis	Antidepressants (paroxetine, bupropion, phenelzine)[51,58]

6.7 Celiac disease, Abdominal Epilepsy, and Acute Interment porphyria

Celiac disease: Celiac disease (CeD) is an autoimmune enteropathy caused by an abnormal immune response to gluten. As per the Indian Council of Medical Research diagnostic criteria, a diagnosis of CeD is based on a combination of clinical manifestations, antibodies to transglutaminase 2 (i.e. positive IgA anti-tTG antibody), and a deep duodenal biopsy demonstrating the presence of at least Marsh grade 2 villous abnormalities.[59]

Individuals with CeD are more likely to develop gastrointestinal and extra-intestinal disorders, including psychiatric disorders. Depression, anxiety, schizophrenia, bipolar disorder, other psychotic illnesses, ADHD, autism, sleep, and eating disorders are the most commonly reported psychiatric disorders among patients with CeD.[60] Furthermore, neuropsychiatric disorders such as gluten ataxia, peripheral neuropathy, and gluten encephalopathy are commonly reported among these patients.[61]

There is evidence to suggest that drug absorption may be increased (e.g. propranolol), delayed, reduced, or normal in CeD; this includes psychotropic medications too.[62] There is little research on the pharmacokinetics of psychotropic medications among patients with CeD. Therefore, while treating psychiatric disorders among patients with CeD, drugs should be used with caution.

Gluten-free diet is the main stay of treatment among patients with CeD. Patients with CeD should be educated to avoid cereals and food products derived from wheat, barley or rye, and food made from gluten-contaminated cereals. A safe gluten intake limit could be set between 10 and 100 mg per day. A gluten-free diet also improves depressive and behavioral symptoms in these patients and increases free L-tryptophan levels.[61]

Abdominal Epilepsy: Abdominal epilepsy is a rare cause of recurring abdominal pain. Characteristic features include paroxysmal episodes of abdominal pain, a variety of abdominal complaints (e.g., vomiting, nausea), definite electroencephalograhic abnormalities, and a favourable response to anticonvulsants.[63] It is more common in children than in adults. Patients who experience recurring abdominal pain are frequently referred for psychiatric evaluation to rule out functional disorders. Therefore, a clinician should assess these patients for the possibility of abdominal epilepsy.

Acute Interment porphyria: Acute intermittent porphyria (AIP) is a rare disorder of heme metabolism characterized by recurrent attacks of abdominal pain, gastrointestinal symptoms, and autonomic nervous system disturbances. Certain drugs, starvation, and infection during pregnancy can trigger AIP attacks. Psychiatric manifestations of AIP include mood swings, psychosis, anxiety, and organic brain disorders. Most mood stabilisers or anticonvulsants (e.g., barbiturates, phenytoin, carbamazepine), agents with sedative properties (e.g. chlordiazepoxide), oral contraceptive pills, and alcohol are contraindicated in patients with AIP. Psychotropic medications such as chlorpromazine, trifluoperazine, diazepam, clonazepam, lorazepam, sertraline, venlafaxine, olanzapine, risperidone, clozapine,

buspirone, trazodone, and morphine are considered safe for treatment of acute attack of porphyria and concurrent psychiatric disorders.[64,65]

7 Conclusion

Psychopharmacology in patients with liver and gastrointestinal disorders must be individualized based on the choice of psychotropic agent and severity of the underlying medical condition**.** In patients with liver disease, it is preferable to use psychotropic drugs that avoid or minimally undergo hepatic metabolism. Caution is required while prescribing any psychotropic drug in severe hepatic disease (Child-Pugh C), as safety data may be lacking. In gastrointestinal disorders, there are few absolute contraindications, but conditions such as gastric bypass and coeliac disease may alter absorption of drugs and reduce therapeutic benefits. Every patient must be assessed for drug-drug interactions and adverse effects. Periodic monitoring of hepatic functions may be required for medications that have a propensity to cause hepatotoxicity. Proper awareness about challenges stemming from co-morbid medical illness can enable successful pharmacologic treatment of psychiatric disorders among the medically ill.

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MANAGEMENT OF PSYCHIATRIC DISORDERS IN PATIENTS WITH STROKE AND TRAUMATIC BRAIN INJURY

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INTRODUCTION

Psychiatric disorders, both short term and long term are common after stroke and traumatic brain injury (TBI). They can be caused by regional disruption of neuronal network, impairment of regional cerebral blood flow, impaired cerebral metabolism, axonal injury and pressure effect of intracranial bleed. Around 16 million people each year experience first ever stroke. Of these patients, 5 million become disabled and 5.7 million dies.[1] Traumatic brain injuries are also common and pose an enormous burden on families and caregivers because of the associated neuropsychiatric complications.[2] However, these neuropsychiatric complications are often remained unaddressed or not adequately treated because of the treating doctor's preoccupation with other severe physical disabilities. Whereas, treating these neuropsychiatric complications can improve the overall outcome of the patients to a considerable extent.

In this clinical practice guideline (CPG) assessment of psychiatric disorders following stroke and TBI are discussed together, while management of psychiatric disorders following stroke and TBI are discussed separately under two broad subheadings. This CPG mostly focussed on the most common non-cognitive neuropsychiatric consequences of stroke and TBI namely depression, psychosis, anxiety, post-traumatic stress disorders (PTSD), mania, emotional lability, fatigue, apathy, and personality changes. There is substantial overlap between neuro-psychiatric disorders following stroke and TBI and repetitions will be avoided. We included researches both on ischemic stroke and intracerebral haemorrhage. However, we did not include dementia.

CATEGORIES OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

While writing this CPG, we ensured compliance with AGREE II instrument. We marked available evidences from Ia to IV and strengths of recommendations from A to D as per the prevailing norms.[3]

I. Categories of evidence

Ia: evidence from meta-analysis of randomised controlled trials (RCTs)

Ib: evidence from at least one randomised controlled trial

IIa: evidence from at least one controlled study without randomisation

IIb: evidence from at least one other type of quasi-experimental study

III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies

IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities

II. Strength of recommendations

A: directly based on category I evidence

B: directly based on category II evidence or extrapolated recommendation from category I evidence

C: directly based on category III evidence or extrapolated recommendation from category I or II evidence

D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

S: Standard of care

ASSESSMENT OF PSYCHIATRIC DISORDERS FOLLOWING STROKE AND TBI

As a referral physician, psychiatrists have the role to make thorough assessment of a patient following stroke and TBI to rule in / out the presence of any psychiatric disorders in a busy emergency room (ER) or inpatient department or intensive care unit (ICU).

To assess the consciousness level of the patient, Glasgow Come Scale (GCS) still remains the gold standard. It is usually very difficult to conduct a psychiatric assessment on a semi-comatose patient or a patient who is uncooperative. In that case, one can use Kirby's proforma for examining uncooperative patients. The attending psychiatrist should examine the patient in a calm environment with not too many people around. However, presence of primary caregiver can be allowed if patient cannot give reliable and valid information which is more often the case. The demeanour of the treating doctor should be non-threatening. He should talk in a clear voice with every word being uttered with due stress to reach the patient who usually have some or the other sensory impairment. If in delirium, psychiatrist should revisit the patient at a later date and time. Psychiatrist should also take the pain to bring forth the history of substance use disorders (SUDs) which are commonly associated with road traffic accidents and resultant TBI.

The treating psychiatrist should go through the clinical records very carefully and if needed should corroborate the clinical history from the primary caregiver or the eye witness(es). Patient's past psychiatric history is of immense importance as it has some correlation with development of post stroke depression (PSD) and other psychiatric disorders. Psychiatrist should also go through the lab reports carefully and look for underlying infection, blood loss, electrolyte disturbances, endocrine dysfunction and other systemic comorbid conditions which are reflected in complete blood count, urine culture & sensitivity, cerebrospinal fluid study, haemoglobin level, serum sodium, serum potassium, serum chloride, serum thyroid stimulating hormone (TSH), serum parathyroid hormone (PTH), fasting blood sugar, liver function test, serum creatinine etc. If needed and when in doubt, the referral psychiatrist should order for more biochemical investigation to rule out organic condition. The psychiatrist should also pay attention to the neuroimaging reports (computed tomography

scan, magnetic resonance imaging etc) to decipher a possible connection between the neurological insult and psychiatric disorder. Electroencephalography (EEG) should be ordered to rule out sub convulsive status epilepticus which can mimic a psychiatric disorder. A detailed scrutiny of the medications already received should be done to rule out any iatrogenic psychiatric disorder. If needed, the psychiatrist should talk to treating neurologist or the neurosurgeon regarding stoppage of medicine, replacing the offending drug, or possible dose adjustment.

A detailed mental status examination (MSE) should be done with particular focus on obtaining a adequate speech sample, looking for the predominant affect, presence of any delusion or hallucination, and assessment of cognitive function particularly judgement, abstract thinking and lobar functions.

There are provisions to diagnose various psychiatric disorders following stroke, transient ischemic attack (TIA) and brain injury in DSM 5 and ICD10. The diagnosis of post stroke and post TBI psychiatric disorders depend on structured clinical interview and using of a screening instrument. There is no universally accepted screening instrument for diagnosing psychiatric disorders following stroke or TBI. For diagnosis of PSD, Hospital Anxiety Depression Scale (HADS), Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), Hamilton Depression Rating Scale (HDRS), nine-item Patient Health Questionnaire (PHQ-9), and the Centre for Epidemiological Studies Depression (CES-D) scale have been used. Anxiety disorders can be screened by Hamilton Anxiety Scale (HAS), Hospital Anxiety and Depression Scale-Anxiety Subscale. For screening of PTSD, psychiatrist can use PTSD checklist for a stressor, TIA or stroke as stressor; Impact of Events Scale-Revised; Post-Traumatic Stress Diagnostic Scale; clinician administered PTSD Scale. Brief Psychiatric Rating

Scale (BPRS) can be used for screening of psychosis and Young's Mania Rating Scale (YMRS) can be used for screening of mania. For assessment of personality disorders or personality changes a detailed psychological evaluation with International Personality Disorder Examination (IPDE), Eysenck's Personality Questionnaire (EPQ), Minnesota Multiphasic Personality Inventory (MMPI) or Iowa Personality Disorder Screen (IPDS) may be needed.

Box 1: Checklist for treating psychiatrist while evaluating post stoke and post TBI psychiatric disorders

1. Patient conscious, alert and cooperative
2. Adequate clinical history
3. Reliable informant who can be a primary care giver or eye witness
4. History of pre-existing psychiatric disorder
5. History of substance use disorders (SUDs)
6. Temporal correlation between stroke/ TBI and onset of psychiatric disorders
7. Biochemical investigations
8. Neuroimaging, EEG
9. Medicine chart
10. BP, Pulse rate, intake-output chart
11. Detailed mental status examination (if uncooperative, Kirby's proforma for examining uncooperative patients should be used)
12. Screening instruments for psychiatric disorders
13. Liaison with neurologist, neurosurgeon

Table 1: Screening tools and management of various psychiatric disorders following stroke / TBI

Clinical Condition	Name of screening instruments	Management
Post-stroke/ post-TBI depressive disorders	• Hospital Anxiety Depression Scale (HADS) • Beck Depression Inventory (BDI) • Geriatric Depression Scale (GDS) • Hamilton Depression Rating Scale (HDRS)	SSRIs, SNRIs & CBT

	• Nine-item Patient Health Questionnaire (PHQ-9) • Centre for Epidemiological Studies Depression (CES-D	
Post-stroke/ post-TBI anxiety disorders	• Hamilton Anxiety Scale (HAS) • Hospital Anxiety and Depression Scale-Anxiety Subscale	SSRIs, SNRIs, TCAs, Yoga, Tai-Chi, Self-help mindfulness, and relaxation techniques
Post-stroke/ post-TBI PTSD	• PTSD checklist for a stressor, TIA or stroke as stressor • Impact of Events Scale-Revised • Post-Traumatic Stress Diagnostic Scale • Clinician administered PTSD Scale	SSRIs, SNRIs, TCAs, antipsychotics, anticonvulsants, anxiolytics, trauma-focussed therapies and CBT
Post-stroke/ post-TBI psychosis	• Brief Psychiatric Rating Scale (BPRS)	Second generation antipsychotics (SGAs) e.g. quetiapine, risperidone and olanzapine, injectable antipsychotics, CBT for hallucination or delusion
Post-stroke/ post-TBI mania	• Young's Mania Rating Scale (YMRS)	Mood stabilisers e.g. valproate, carbamazepine, oxcarbazepine etc.; antipsychotics e.g. olanzapine, quetiapine, risperidone etc. and benzodiazepines
Post-stroke/ post-TBI personality disorders	• International Personality Disorder Examination (IPDE) • Eysenck's Personality Questionnaire (EPQ) • Minnesota Multiphasic Personality Inventory (MMPI) • Iowa Personality Disorder Screen (IPDS)	Fluoxetine, citalopram, lithium, beta-adrenergic antagonists
Post-stroke fatigue	• Fatigue Severity Scale (FSS) • Multidimensional Assessment of Fatigue (MAF) • Visual Analog Scale–Fatigue (VAS-F)	Modafinil, regular physical exercises
Post-stroke apathy	• Apathy Scale • Apathy Evaluation Scale	Nefiracetam, donepezil, bromocriptine, modafinil, methylphenidate, ropinirole and zolpidem

MANAGEMENT OF POST-STROKE PSYCHIATRIC DISORDERS

A. Post-Stroke Depression (PSD)

PSD is the one of the most commonly reported neuropsychiatric conditions following stroke. Often undiagnosed, PSD is a treatable condition. PSD can occur within 1 to 18 months following stroke and its prevalence vary considerably over time (reported prevalence at 1, 3, 6, 12, and 18 months were 24.5%, 27.1%, 28.3%, 19.8%, and 26.3% respectively).[4]

PSD is believed to be associated with worse functional outcome following stroke. A meta-analysis showed that, PSD had a negative impact on survival rates following stroke and it affected short-term mortality more than long-term mortality.[5]

Various meta-analysis and systematic review have looked into the role of prophylactic antidepressant treatment to reduce the chance of developing PSD [6-9]. Many of them found that, selective serotonin reuptake inhibitors (SSRIs), cognitive behavioural therapy (CBT), as well as physical exercise improved mood symptoms in PSD.

A Cochrane review which included 63 RCTs and over 9000 participants and specifically looked into the role of SSRIs in PSD found that, SSRIs should not be used routinely to promote recovery after stroke as they do not improve recovery after stroke (A).[10] In the FOCUS (Effect of fluoxetine on functional outcomes after acute stroke) trial, eligible patients with stroke (but not PSD) were recruited and randomly given fluoxetine (20 mg daily) or placebo for 6 months, starting after 2 to 15 days of stroke. After 12 months of follow up, fluoxetine was found to improve the neuropsychological scale score but not other variables. Therefore, it did not support the routine use of prophylactic fluoxetine in PSD (A).[11]

Similar was the finding from TALOS study (the efficacy of Citalopram Treatment in Acute Stroke) (A).[12]

The efficacy of CBT on PSD remains inconclusive due to high degree of heterogeneity and low quality of the studies that was included in one metanalysis (A).[13] Neuromodulation techniques such as transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) can offer some benefit but there are lack of high quality RCTs (B).[14]

SSRIs and SNRIs are often used in conjunction with anti-platelet medication like clopidogrel in PSD. CYP2C19 inhibiting SSRIs e.g. fluoxetine and fluvoxamine can reduce the efficacy of clopidogrel and can increase the risk of ischemic disease.[15] There have been concerns regarding intracranial bleed following use of SSRIs also. Studies have suggested that, exposure to SSRIs before stroke was associated with severity and mortality in patients with haemorrhagic stroke.[16] However, one recent review suggested that, high quality evidence in support of SSRIs alone increasing the risk of spontaneous intracranial bleed is lacking.

Therefore, *it can be concluded that, SSRIs should not be prescribed prophylactically in all post-stroke patients. Rather, they should be screened for PSD and if diagnosed, then only SSRIs and SNRIs can be prescribed as needed (S) with some sort psychological intervention (CBT) (B).* Both neurologists and psychiatrists need to be aware of drug-drug interaction which can be potentially life threatening in such group of patients (S).

B. Post-Stroke Psychosis (PSP)

Symptoms of PSP include delusions, hallucinations, psychomotor agitation, irrelevant and incoherent speech, catatonic symptoms, and sleep cycle disturbances. These symptoms usually manifest within a week following stroke but may manifest several weeks later also.

Studies form early 90s indicated that PSP is relatively rare and after 9 years follow up only 5 patients developed PSP.[17] A recent meta-analysis found the prevalence of PSP to be around 4.86%.[18]

Literature on management of PSP is sparse compared to PSD or post-stroke anxiety (PSA). RCTs on management of PSP is lacking. Treatment usually follows same principles which are followed for management and treatment of primary psychotic disorders. *Second generation antipsychotics (SGAs) e.g. quetiapine, risperidone and olanzapine are most commonly used to treat PSP* (D). However, their safety in patients with stroke is highly debatable. Olanzapine can have deleterious effect of plasma glucose and lipids which are not welcome in patients with stroke. Quetiapine can cause postural hypotension, whereas risperidone can cause extra-pyramidal side effects. The concern of anti-psychotics being associated with high incidences stroke has been refuted by a large case-control study. [19-21]

The usual practice is to start low and go slow in case of treatment of PSP (S). But, in certain cases (agitated and violent patients) injectables might be required and in that case injectable olanzapine or injectable haloperidol can be used (D). As in patients with primary psychotic disorders, CBT for hallucination or delusion can be beneficial in PSP (S).[22]

C. Post-Stroke Anxiety Disorders (PSA)

PSA is common and only second to PSD in terms of prevalence. All kind of anxiety disorders can be seen following stroke but the core symptoms remain the same – palpitation, psychic and physical restlessness, excessive worry and fear, feeling of nervousness, pseudo neurological symptoms e.g. dizziness, blurring of vision, tingling and numbness of hands and feet, fine tremors etc. Sensory impairment, intensive care unit (ICU) admission, painful physical conditions, communication difficulties, and sleep disturbance can lead to

development of PSA (59). A meta-analysis found prevalence of PSA to vary between 20% to 24% depending on the time elapsed following stroke.[23]

SSRIs, SNRIs, Tri-Cyclic Antidepressants (TCAs), Mirtazapine, Buspirone, Benzodiazepines, Z-drugs all have been used in the treatment of PSA in the absence of any definite guideline (D). [24] Meta-analyses conducted by Chun et al reported beneficial effect of pharmacotherapy (paroxetine, imipramine and buspirone) and psychotherapy compared to control. But the studies were of low quality and highly heterogenous and therefore the positive conclusion could be due to bias.[25] Cochrane review in this area also highlighted lack of quality studies and emphasised the need of large scale RCTs.[24] *Non-pharmacological managements e.g. Yoga, Tai-Chi, Self-help mindfulness, and relaxation techniques can offer some benefit in the management of PSA (C)*.[26,27]

Therefore, *SSRIs, SNRIs, and even TCAs can be used in the treatment of PSA (S,D) along with non-pharmacological interventions (C)*. However, as in case of PSD, psychiatrists and neurologists should be aware of potential drug-drug interactions.

D. Post-Traumatic Stress Disorder (PTSD) following Stroke

PTSD is a condition that develops following an event which pose actual or imagined threat to physical and psychological integrity of an individual and stroke is no less than a catastrophe. Symptoms of PTSD include intrusive flashbacks/ memories, autonomic arousal, emotional numbness, and avoidance behaviour. Post stroke PTSD often have associated PSD and PSA (in up to 40% of the cases).[28] A meta-analysis reported one year prevalence of post stroke PTSD to be around 23%.[29] Also, persons with PTSD have higher risk of developing stroke compared to people without PTSD.[30]

There is dearth of RCTs in treatment of PTSD. *SSRIs, SNRIs, and TCAs can be tried (D). Other medications e.g. antipsychotics, anticonvulsants, and anxiolytics have also been tried (D)*.[31] Psychotherapeutic approaches e.g. trauma-focused therapies, CBT, and exposure therapy appears to be helpful in resolution of symptoms but they need to be tested in large scale studies (D).[32]

E. Post-Stroke Mania (PSM)

Prevalence of post stroke mania is rather low (<2%).[33] Most of the data in this area are in the form of case report or case series.[33] Majority of the subject developed PSM between 1 day to 24 months after stroke.[33] In 1978, Kraut-hammer and Klerman introduced the concept of secondary mania.[34] This term refers to the onset of symptoms that meet the diagnostic criteria for mania produced by neurological, metabolic, or toxic disorder. The criteria of secondary mania (PSM in this case) is as follows: 1) symptoms duration of at least 1 week; 2) presence of elevated or irritable mood; 3) presence of at least two of the following symptoms: hyperactivity, pressured speech, flight of ideas, grandiosity, decreased sleep, distractibility, and lack of judgment; and 4) no history of manic depressive or other affective illness and symptoms of a confused state (such as delirium) co-occurring with the mania.4 Lesions responsible for poststroke mania are usually located in the thalamus, caudate nucleus, and temporal, parietal, and frontal lobes. Mania seems to be more associated with right-sided lesions, although left sided lesions have also been reported.[35,36]

Treatment of PSM is in line with treatment of an acute manic episode. *Mood stabilisers e.g. valproate, carbamazepine, oxcarbazepine etc.; antipsychotics e.g. olanzapine, quetiapine, risperidone etc.; and benzodiazepines are the mainstay of treatment (S. D)*. It is better to

avoid lithium in this population because of presence of multiple comorbidities and potential drug-drug interactions. Also choosing a mood stabiliser which allows antiepileptic coverage is beneficial.

F. Post-Stroke Emotional Lability

Post stroke emotional lability is also known by various other names e.g. pathological laughter/ crying, emotional incontinence, hyperemotionality, pseudobulbar affect etc. Symptoms appeared to be dramatic but transient. Patients can present with sudden onset laughter or crying while speaking on a rather inconspicuous matter. Sometimes it may be difficult to differentiate it from depression. If symptoms are long-lasting it may result in distress, depression, social avoidance and embarrassment. The prevalence of post-stroke emotional lability varies between 8% to 32%.[37]

Quality research in the treatment of post-stroke emotional lability is lacking, thereby precluding any meaningful recommendation. *A Cochrane review of seven trials with total 293 participants reported that, antidepressants reduced the frequency of laughing and crying episodes but the quality of evidence was low (A)*. The effect was not specific to any particular drug or class of drugs. The review pointed our several methodological deficiencies.[38]

G. Post-Stroke Fatigue (PSF)

PSF is a common sequalae of both ischemic and haemorrhagic stroke. Nearly half of the stroke survivors suffer from PSF. A systematic review put the prevalence of PSF between 25% to 85%.[39] However, there is no unform definition of PSF. Most commonly PSF is described as, subject lack of physical and mental energy which interferes with individual's

day to day activities. Post stroke fatigue has been found to be associated with old age, neurological deficits, diabetes, hypertension, heart failure, kidney disease, sleep disturbances, pain, pre-stroke fatigue, depression, anxiety, and cognitive impairment.[40] Few studies have suggested a link between PSF and subcortical and infra-tentorial infarcts.[40]

Considering the multifactorial causation of PSF, any one particular pharmacological agent is unlikely to provide any benefit. *Modafinil, a mood awakener has been found to be useful in PSF following brainstem-diencephalic stroke because of its effect on reticular activating system (C)*.[41] A small RCT also favoured the use of Modafinil up to a dose of 400 mg/day (B).[42] SSRIs including fluoxetine, escitalopram, sertraline and SNRI, duloxetine has been studied in PSF but none were proven beneficial except for anxiety symptoms.[43,44] Clinicians often try vitamin supplementations in PSF. Vitamin B12, vitamin B1, and idebenone, a synthetic coenzyme Q10 analogue have all been studied but results are inconclusive (C).[45-47] *Joint American Stroke Association and American Heart Association statement encourages regular physical exercise to reduce PSF (D, S)*.[48] A Cochrane review which included 2 nonpharmacological interventions, a fatigue education program, and a mindfulness-based stress reduction program found that, there was no conclusive evidence of any intervention having any efficacy to treat or prevent PSF (A).[49]

H. Post-Stroke Apathy

Post-stroke apathy has been reported as a frequent consequence of stroke. It is defined as a lack of goal directed behaviour along with diminished cognition and emotion. appetite). Recently proposed diagnostic criteria for post-stroke apathy includes, a) diminished motivation (core feature) for four weeks or more, and two other symptoms (reduced goal-

directed behaviour, goal-directed cognitive activity, or emotions), and functional impairments.[50] There are conditions, particularly depression, which can mimic post-stroke apathy. In that case, emphasis should be put on presence / absence of cognitive symptoms of depression e.g. low mood, anhedonia, lack of attention & concentration, negative cognition, suicidal ideas etc. A large meta-analysis found that, mean prevalence of post-stroke apathy was 34.6%.[51] Post-stroke apathy is more common in women, less educated subjects, cognitively impaired, and in cases of recurrent stroke.[52] Apathy and depression co-occur in about 40% of cases.[51] Patients with apathy has been found to have worse functional outcome and higher risk of subsequent depression.[53]

Quality evidence for the treatment of post-stroke apathy is lacking. There is one RCT with *Nefiracetam* (600 mg & 900 mg dose) which resulted in 4-point decrease in Apathy Scale score and more frequent remission(B).[54] Acetyl cholinesterase inhibitor, *Donepezil has been found to have some benefit in post-stroke apathy in a retrospective cohort study (C).*[55] There are *anecdotal evidences of bromocriptine, modafinil, methylphenidate, ropinirole and zolpidem being effective in treating post-stroke apathy in various case-reports* (C).[51]

I. Post-Stroke Personality Disorders

There can be exacerbation of pre-existing personality traits or patient can altogether develop new personality after a stroke. There are possibilities that patient becomes irritable/ aggressive, disinhibited and /or impulsive. Personality changes are more prominent in case of frontal lobe lesions. Studies have put the prevalence of irritability and disinhibition at 12%-53% and 6%-76% respectively. [56,57] The wide variability in prevalence

was because of the setting in which the study was conducted, population chosen, type of stroke, and instruments used to assess personality changes.

There are very few RCTs which have looked into the treatment of post-stroke personality disorders per se. Data have been extrapolated from studies conducted in non-stroke individuals. SSRIs e.g. *fluoxetine and citalopram can be beneficial for treatment of aggression in patients with personality disorders post-stroke* (D).[58,59] *Lithium and beta-adrenergic antagonists may also be effective to treat aggression* in this group of patients (D).[60,61]

MANAGEMENT OF PSYCHIATRIC DISORDERS FOLLOWING TRAUMATIC BRAIN INJURY

For management of psychiatric disorders following traumatic brain injury (TBI) we are not going to follow the same schema for stroke for brevity of this clinical practice guideline (CPG). Rather, we will highlight upon important management issues and treatment evidences as deemed fit.

The first documented report of psychiatric disorder following TBI was of a construction worker called, Phineas Gage who survived an accident in 1848, when an iron bar went through his skull and damaged his frontal lobe which changed his personality form a responsible, socially adapted man to negligent, profane and not willing to take responsibility.[62]

Host of psychiatric disorders can be seen following TBI. Post-traumatic agitation, aggression and irritability are common in the coma-awakening period. Post-traumatic agitation has been related to post-traumatic amnesia, altered consciousness and decrease in cognitive function. The incidence of post-traumatic agitation varies between 11% to 70%.[63] Pain,

ongoing medications, sleep deprivation, and underlying delirium can promote agitation. Aggression can be verbal aggression and physical aggression towards self and others. More often than not aggression is sudden and episodic in nature.[64] The extent of aggression is dependent upon the severity of initial injury and extent of prefrontal damage.[65] The incidence of aggression in TBI varies between 25 % to 39%. [66] Irritability is although a rather muted form compared to agitation and aggression, it is common in post-TBI patients which manifests as excessive reaction with unjustified anger. The incidence of post-TBI irritability varies between 29% to 71% as per the nature of the studies conducted.[67]

Other disturbing consequences of TBI are apathy, abulia, and apragmatism. We have discussed apathy in detail in the section of psychiatric disorders following stroke. The prevalence of post-TBI apathy varies between 20% to 71%.[68] As discussed earlier, apathy can be difficult to differentiate from depression. Also, apathy can respond poorly to available pharmacological options.

Depression, anxiety and psychosis are other common psychiatric disorders following TBI. The mean prevalence of depression after TBI was found to be 7.5 times higher compared to general population and was put at 30%.[69] Being young, female, having depression at the time of suffering injury, pre-existing cognitive deficits, lesion of left hemisphere (particularly basal ganglia and dorso-lateral prefrontal cortex and pain was associated with depression in TBI patients.[70] All kinds of anxiety disorders, e.g. generalised anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, PTSD, obsessive compulsive disorder are common in TBI patients. The prevalence of anxiety disorders has been found to vary between 5.8% to 9.1%.[71] Association between psychosis and TBI is less clear. A meta-analysis suggested that, risk of schizophrenia was higher in TBI group compared to control

group but heterogenicity of studies included precluded any meaningful conclusion.[72] Suicidal ideation and attempts have been found to be higher in TBI group compared to general population and some researchers have found it to be as high as 3-4 times.[73] Around 20% subjects with TBI expressed suicidal ideation.[74-76]

Almost all kinds of psychopharmacological agents e.g. mood stabilisers, antidepressants, antipsychotics, dopamine agonists, benzodiazepines, beta blockers, opioid receptor antagonists have been tried in the management of psychiatric disorders following TBI (Table-2), but in the absence of robust study design and large sample size of the studies included, recommendations are difficult to make.[77-109] In clinical practice, many of these agents produce desired result, albeit temporarily, alone or in combination. There is scant evidence in favour of non-pharmacological treatment. One Cochrane review did not find any compelling evidence in favour of any non-pharmacological intervention e.g. cognitive behavioural therapy or mindfulness-based cognitive therapy for depression following TBI.[110] There are certain things a psychiatrist should be aware while handling such patients e.g. level of consciousness, baseline cognitive function, neuroimaging findings, operative procedures done or pending, presence or absence of clinical seizure, sub convulsive status epilepticus, medications received by the patient, drug-drug interaction, family support etc (Box-2). Minimum number of medications for minimum period should be prescribed to improve patient compliance (S). Benzodiazepines (oral or intramuscular) should be judiciously used because of risk of fall, fracture and cognitive deterioration (S). Last but not the least, attending psychiatrist should also use his own judgement depending on presence/ absence of comorbid physical conditions.

Box 2: Points to remember for treating psychiatrist in patients with TBI

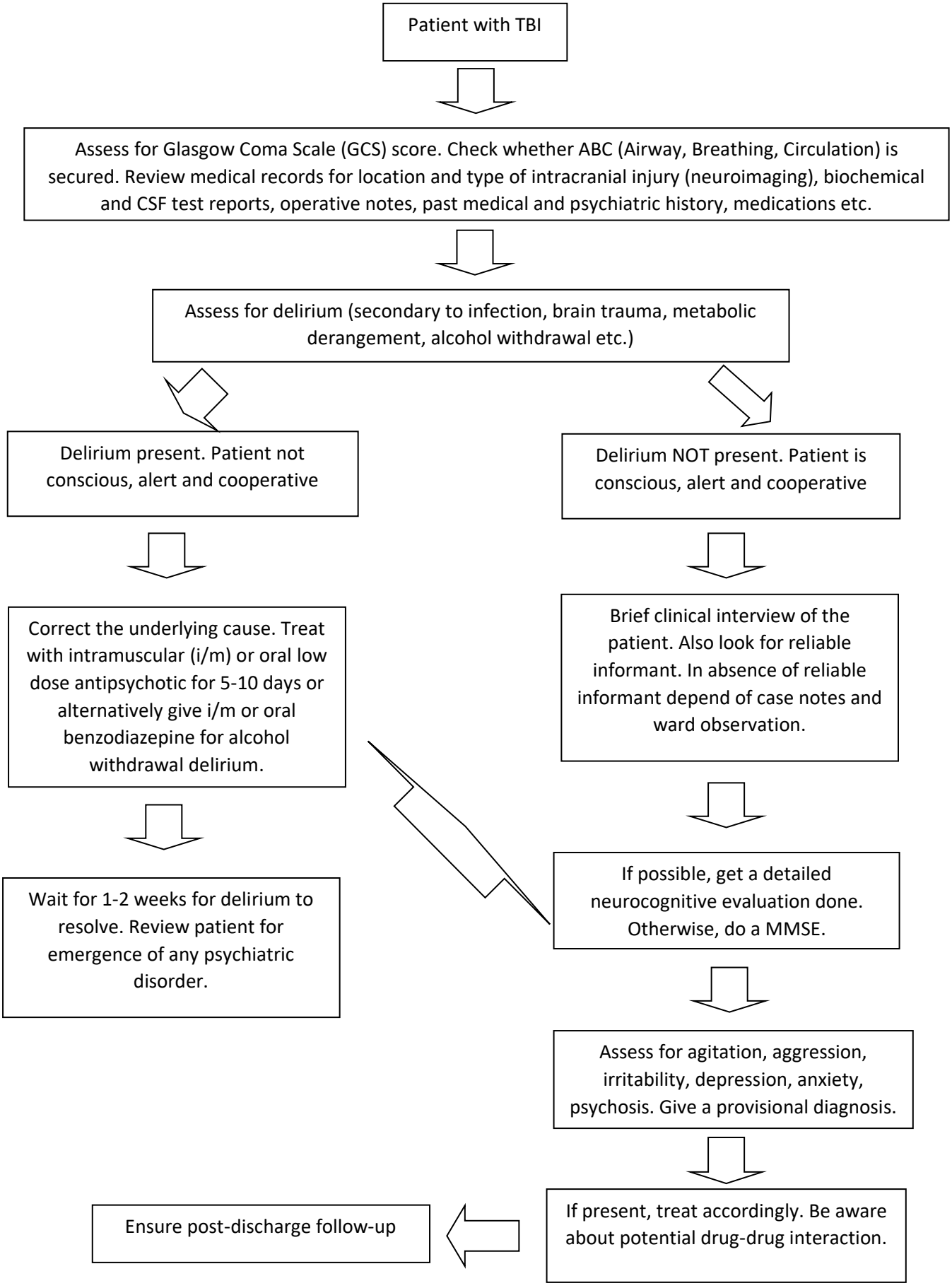
1. Assess level of consciousness of the patient. Do a Glasgow Coma Scale (GCS) scoring (S)
2. Enquire about post-TBI loss of consciousness, ear-nose-throat (ENT) bleed, seizures
3. Try to understand the nature of problem. It may be different for the patient and the caregiver
4. If possible, get a baseline neuro-cognitive assessment done. In absence of the same, do a Mini Mental State Examination (MMSE) (S)
5. Go through neuroimaging and EEG reports
6. Go through the medications which he/she is already on
7. If patient underwent neurosurgery, go through the OT (operation theatre) notes/ discharge notes
8. Mention your clinical diagnosis or at least the provisional diagnosis. It may be required later because of medico-legal issues associated with such cases (S)
9. Choose medication in such a way that it covers neurological issue and psychiatric issue simultaneously e.g. in a patient with seizure and aggression following TBI one can choose valproate which will be effective for both the conditions (S)
10. Always encourage healthy lifestyle, exercise and mental activities
11. Assess for substance use disorders (SUD). If present, treat it like a case of dual diagnosis

Table 2: Pharmacological agents used to treat psychiatric disorders following TBI and their strength of recommendation

Name of the molecule	Dose range	Clinical effect	Strength of recommendation
Methylphenidate (MPH) [77]	3mg/kg, two times daily	Increased the speed of information processing in Several neuropsychological tests	B
Agomelatine [78]	25 mg at night	Increased efficiency of sleep	C
Modafinil [79-81]	300-600 mg/d	Improvement in fatigue but no improvement in excessive daytime sleepiness	A
Amantadine [82,83]	100 mg twice daily	Reduced frequency and severity of aggression and irritability	A
Valproate [84,85]	1000-2000 mg/day	Improvement in mood symptoms. Valproate should not be used prophylactically for post-traumatic seizures	B
SSRIs [86-90]	Variable dosages	Citalopram and sertraline should not be used for prevention of relapse of depressive symptoms after TBI. Use of fluoxetine for six months in patients with post-traumatic stress decreased relapse rates. MPH and sertraline had similar effects on depressive symptoms, however, MPH caused more improvement in cognitive functions	B
Venlafaxine [91]	75 mg twice daily	Improved obsessive-compulsive symptoms, irritability and sadness	C
Bromocriptine [92]	5 gm, twice daily	Did not improve alertness, was associated with side effects	B
Rivastigmine [93]	3-6 mg/d	Was beneficial for moderate to severe memory impairment	B
Galantamine [94]	16-24 mg/d	Improved fatigue, initiative, attention and memory	B

Donepezil [95,96]	10-20 mg/d	Improved metabolism in all 4 lobes of brain, overall clinical improvement and memory improvement	B
Naltrexone [97,98]	50-100 mg	Improved initiation, attention and accuracy of answering non-verbal questions	C
Beta blockers (Propranolol) [99,100]	420-520 mg/d	Number of attempted assaults and agitated episodes decreased	A
IM Droperidol & Haloperidol [101,102]	IM Droperidol 1.25-10 mg & IM Haloperidol 2.5-10 mg	IM Droperidol achieved faster calming compared to IM Haloperidol	B
Clozapine [103]	300-750 mg	Marked decrease in aggression	C
Quetiapine [104]	25-300 mg	Reduction in aggression	B
Ziprasidone [105]	40-80 mg	Decrease in agitated behaviour	C
Carbamazepine [106]	400 -800 mg	Improvement in social disinhibition and agitation was noted	B
Lamotrigine [107]	50 mg	There was decreased need for benzodiazepines to control outburst	C
Lithium [108]	900 mg/d	Decreased requirement of neuroleptics and decreased in aggression	C

Figure 1: Flowchart of psychiatric management of a patient with traumatic brain injury



Conclusion

Psychiatric disorders following stroke and TBI present unique challenges for the treating psychiatrist. Being a physician who is dealing with brain disorders, psychiatrists of twenty first century should possess in depth knowledge of brain pathways, neurotransmitters and its function. On the other hand, being a behavioural scientist, he/she should be sensitive towards the disability of the patient, the need of the caregivers, and empathetic towards the emotional need of both. The link between psychiatric disorders following stroke and TBI is not an uncomplicated one. Therefore, treatment also needs to be individualised. No one drug fits for all. Psychiatrist often has to do permutation and combination before he/ she finds the suitable match. As already been highlighted, there is dearth of large scale RCTs for most of the conditions and treatment recommendations are often extrapolated from primary psychiatry disorders. But that always may not work. Because a compromised or injured brain may not function in the same way as a 'normal' or 'uninjured' brain. Still, this guideline made an attempt to collate majority of the available evidences in this area and recommendations were made based on those evidences. Reader has to apply his/ her own judgement while implementing this is in a particular clinical setting.

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MANAGEMENT OF PSYCHIATRIC DISORDERS IN PATIENTS WITH PARKINSON'S DISEASES

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ABSTRACT

Parkinson's Disease (PD) is a heterogenous progressive neurodegenerative disorder with the triad of motor symptoms with akinesia/bradykinesia, resting tremor (4-6 Hz), and rigidity. It is the second most common neurodegenerative disease after Alzheimer's disease. The overall management of PD depends on the status of symptoms, functioning of the patients, impairment, disability, and its impact on quality of life. Depression, anxiety disorders, apathy, anhedonia, psychosis, cognitive impairments, dementia, and impulse control disorders are the common psychiatric symptoms/ disorders comorbid with PD. Depression remains the most common psychiatric disorder reported to be comorbid with PD. Several pharmacological and nonpharmacological management strategies are used for the treatment of comorbid psychiatric disorders in PD. Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors are used to treat depression in patients with PD. The best evidence of efficacy in PD psychosis is for Clozapine and pimavanserin. The treatment for cognitive impairments in PD remains poorly researched. Rivastigmine is the only approved treatment for PDD as per Food and Drug Administration (FDA). Pramipexole, a dopamine agonist, is reported to cause improvement in the symptoms of decreased willingness in apathy. The treatment approaches for different sleep disorders in PD are different. Identifying the cause, reviewing the patient's ongoing medications, evaluating the impact of comorbid medical conditions, and sleep hygiene are common to all conditions related to sleep disorders. The first approach for treating ICD Impulse Control Disorder symptoms is the reduction or discontinuation of dopamine agonists. The psychiatric symptoms in patients with PD are highly prevalent, and their management should be included in the basic treatment algorithm for Parkinson's disease. This paper summarizes common psychiatric symptoms/disorders in Parkinson's disease and their management approaches.

1. INTRODUCTION

Parkinson's Disease (PD) is a heterogenous progressive neurodegenerative disorder. It originates primarily from the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Akinesia/bradykinesia, resting tremor (4-6 Hz), and rigidity are the triad of motor features and are hallmarks of the disease. The other characteristic clinical manifestations include gait (festinating) and postural abnormalities.

The classic motor symptoms of Parkinson's disease and the other common non-motor clinical features are elaborated in table-1 [1,2].

Table 1: Clinical characteristics of Parkinson's disease

Motor symptoms	• Resting tremor (4-6 Hz), rigidity, bradykinesia, postural instability • Hypomimia ("masked facies"), softer and monotone speech, dysphagia, dysarthria, sialorrhea. • Shuffling gait, decreased arm swing, festination, difficulty turning in bed, arising from chair, slowness in activities of daily living, micrographia. • Glabellar reflex, striatal deformity, scoliosis, blepharospasm, dystonia etc.
Nonmotor symptoms	• Cognitive impairments, dementia, depression, anxiety disorders, apathy, anhedonia, psychosis, impulse control disorders and other psychiatric disorders. • Sensory symptoms: anosmia, ageusia (loss of taste), pain (shoulder, back), paraesthesia. • Dysautonomia (urinary symptoms, constipation, orthostatic hypotension, and sexual dysfunction, seborrhoea, abnormal sweating), weight loss. • Sleep disorders (insomnia, excessive daytime sleepiness, restless leg syndrome, REM sleep behavior disorder, obstructive sleep apnoea and other sleep disorders

2. Non-motor symptoms and psychiatric syndromes in PD:

This paper describes features and management of following common psychiatric symptoms/disorders in Parkinson's disease.

- Depression
- Anxiety
- Psychosis
- Cognitive impairments and dementia
- Apathy
- Sleep related disorders
- Impulse control disorders

2.1. Patients with Parkinson's disease have been reported to have a high rate of depression. In fact, there is a vicious cycle between depression and Parkinson's disease, with the presence of one increasing the risk of the other. As a result, depression is considered a risk factor for Parkinson's disease; despite this, it is neither indicative nor predictive of progression motor symptoms in PD patients.

2.2. Anxiety is also a prevalent symptom in PD and the second most common psychiatric disorder after depression.[3]. Anxiety has also been reported as a predictor of Parkinson's disease even when caffeine intake, smoking, and anxiolytic medication had been controlled for [4]. Some studies reported that increased frequency of anxiety disorders could be observed up to 20 years before PD onset [5]. Due to diagnostic imprecision, symptoms overlap with motor and various other reasons, anxiety symptoms/disorders are often under-recognized and under-treated in patients with PD. Anxiety symptoms/disorders in PD patients are categorized into primary and secondary anxiety disorders. Secondary anxiety disorders include anxiety caused secondary to the limitations and impairment caused by PD, to other psychiatric comorbidities (e.g., depression, psychosis), to the fluctuation of motor symptoms (on/off periods), anxiety secondary to the use of anti-parkinsonian medications (e.g., levodopa, pergolide, etc.) and anxiety as a prodromal symptom of PD [6]

2.3. Psychotic symptoms in patients with Parkinson's disease are characterized as a separate clinical entity having a different clinical presentation and course than schizophrenia, acute psychosis, or other psychotic disorders. It is conceptualized as the "development of hallucinations and delusions during the clinical course of Parkinson's disease" and has implications for staging the disease development and its management. It is

associated with overall poor prognosis, disease burden and even death. The combined National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Mental Health (NIMH) workgroup provisionally described termed it as Parkinson's disease psychosis (PDP). The NINDS-NIMH workgroup concluded that the various phenomenon occurring in PDP are not just a distinct symptom class but also a continuum representing the overall progression of the Parkinson's disease process. This continuum or spectrum of positive symptoms was called 'PD Psychosis' (PDP), and the given diagnostic criteria included its chronology and duration of the symptoms.

2.4. Cognitive dysfunctions are common and can potentially occur at any disease stage of PD [7]. Like depression and anxiety, these dysfunctions might precede the disease onset of PD and can occur during the early stage or at the late stage of the PD. Deterioration of cognitive abilities is progressive, and the incidence and prevalence of cognitive dysfunctions increase with the progression of PD. The cognitive impairments in PD significantly affect the functioning and quality of patients' lives and are one among the high priority areas for the patients and their caregivers. The cognitive dysfunctions prevalent in PD are progressive and may manifest as subjective cognitive decline (SCD), mild cognitive impairment (PD-MCI), or dementia (PDD) (table-2)

Table 2- Common definitions of cognitive impairments in Parkinson's disease

DYSFUNCTIONS	DEFINITIONS
Subjective cognitive decline (SCD)	Self-perceived decline in cognitive ability. However, age, sex, and education-adjusted performance on standardized cognitive tests is normal.
Mild cognitive impairment (PD-MCI)	Gradual deterioration in cognitive ability is reported by either a patient with PD or a caregiver or observed by the clinician. Objective cognitive deficits on either formal neuropsychological test or on a scale of global cognitive abilities are demonstrated. These dysfunctions are causing significant impairments of functioning. PD-MCI can be classified

	based on number of cognitive abilities involved as single or multiple domains.
Parkinson's Disease Dementia (PDD)	Cognitive impairments with deficits in at least two out of four cognitive domains (executive functioning, attention, visuospatial abilities, and memory) significantly affecting normal functioning, which cannot be explained by impairment caused by PD-related motor and autonomic symptoms. Depending on the level of impairments in daily functioning, it can be classified as mild, moderate, or severe. Generally, dementia developing in the context of well-established idiopathic Parkinson's disease (after at least 1 year of motor symptoms) is diagnosed as PDD.

2.5. Apathy is another distinct clinical syndrome in Parkinson's disease as half of the patients have standalone apathy, without depression or cognitive impairment. Apathy can be described as marked decreased interest and participation in what is considered as normal goal-directed behavior, a lack of initiative with difficulties initiating or completing an activity, and indifference or a lack of concern [8]. Hence, apathy, depression, and cognitive dysfunctions need to be separately diagnosed [9]. Apathy syndrome is a separate morbid state with remarkable apathy, occurs over an extended duration. Depression is commonly referred to as an "affective disorder." Apathy is classified as a "motivational disorder" distinct from affective disorders, and emotion is flattened in apathy[10].

2.6. Sleep disorders are among the common nonmotor symptoms found in PD. Some sleep disorders in PD, such as rapid eye movement (REM) sleep behavior disorder (RBD) are seen to have a specific association with PD and may occur several years before PD. The various types of sleep disorder in PD and their clinical features, along with their prevalence, are mentioned in table-3 [11,12].

Table 3: Types of sleep disorder in Parkinson's Disease and their clinical features with their prevalence.

	SLEEP DISORDER	CLINICAL FEATURES	Prevalence
1.	Insomnia	Difficulty in (i) falling asleep, (ii) maintaining the sleep, and (iii) early morning awakenings	27 to 80%
2.	Excessive daytime sleepiness (EDS)	Excessive unintended sleep during Daytime	13–47%
3.	REM sleep behavior disorder (RBD)	Dream enactment leads to screaming, crying, laughing, talking, violent limb movements during sleep, risk of injury to the patient and bed partner.	22–60%
4.	Restless legs syndrome (RLS)	Urge to keep the legs moving, not always associated with unpleasant sensations. Symptoms are more during periods of rest or inactivity, and patients get relief by moving the legs.	8–35%.
5.	Obstructive sleep apnoea (OSA)	Loud snoring, abrupt awakenings accompanied by choking, excessive daytime sleepiness, fragmented sleep and frequent nocturnal awakenings.	20-60%

2.7. Impulse Control Disorders (ICDs) are also commonly observed in PD. These are characterized by pleasurable behaviors performed repetitively, excessively, and compulsively. The Diagnostic and Statistical Manual (DSM-5) placed impulse control disorders (ICDs) in the chapter "Disruptive, Impulse-Control, and Conduct Disorders" as dysregulation of self-emotional and behavioral control. ICDs have recently been sub-classified as ICD groups and ICD-related disorder (ICDs-RD) groups. There are three core features of ICDs groups and ICD- related disorders: the presence of impulsivity aspects (lack of forethought or consideration of consequences), the presence of compulsivity (repetitive behaviors with a lack of self-control) and a negative or harmful behavior pattern to oneself or to others.

All these psychiatric disorders in PD are related to patients' impaired quality of life and are also associated with higher caregiver distress [13,14].

3. EPIDEMIOLOGY

Parkinsonism is the second most common neurodegenerative disease following Alzheimer's disease. Over 1 percent of the population over age 55 and approximately 3 percent of the population over age 70 suffers from PD. Incidence and prevalence of PD increase with advancing age. Few studies estimated 10 million people globally (i.e., approximately 0.3% of the world population) suffer from PD [15]. The nationwide epidemiological data from India is not available. The estimated prevalence in India was roughly 10% of the global burden, that is, 5.8 lakhs [16]. From India, crude prevalence rates between 6 and 53/100,000 have been reported. Above the age of 60 years, the reported PRs were higher and were found to be 247/100,000 [17].

3.1. The prevalence rates of depression in PD patients vary from 2.7% to 55.6%. Epidemiological data from some studies suggested the frequency of major or more severe depression is 5–20%, with minor depression present in 10–30% of patients and dysthymia in 22.5% [18–22].

3.2. Anxiety symptoms or disorder are experienced by nearly 3.6% to 40% of PD patients[3]. Among the various anxiety disorders, the most frequent one is generalized anxiety disorder (14.1%), followed by social phobia (13.8%), anxiety NOS (13.3%), and panic disorder with or without agoraphobia (6.8%) [14]. Anxiety and depression are highly comorbid. They co-occur in up to 80% of patients. Apathy is observed up to 40% of PD patients.[9,23]

3.3. PDP is primarily seen in people over 50, with incidence and prevalence increases with age. Studies have shown that up to 60% of PD patients will develop psychosis within 12 years of onset of PD, while in some studies it has been reported early as 19th months of the diagnosis among 27% of the patients[24]. More commonly reported symptoms consist of minor phenomena like hallucinations and visual illusions that have been reported to impact 17 to 72% of patients. Less commonly reported symptoms to include other hallucinations (Auditory and tactile) and delusions.

3.4. The reported prevalence of cognitive dysfunctions in PD vary widely. The reported point prevalence of dementia in PD is around 30%, and rates are up to two to six times more common in comparison to healthy control populations. The overall cumulative prevalence has been reported to be as high as up to 75-80% in patients with 10-year survival of onset of motor symptoms in dementia[25,26].

3.5. The prevalence of the common sleep disorders in PD are mentioned in table 3. A study found that nocturia was the most prevalent of the various nocturnal symptoms in PD (91.5%), and hallucinations were the least common (15%)[11].

Many other non-motor symptoms such as cognitive impairment, psychosis and ICDs have been reported to have a strong association with RBD [13].

4. ETIOPATHOGENESIS

PD is a neurodegenerative disorder referred to as synucleinopathy. The hallmark pathology includes progressive degeneration of dopaminergic neurons in the SNpc and α-synuclein protein aggregation in the form of characteristic Lewy bodies in the surviving neurons.

The motor symptoms in PD are seen when dopamine production is inadequate after a critical degree of neuronal loss and approximately 60 to 80 percent neuronal loss has occurred. The exact causes of PD remain unclear, and how these Lewy bodies are linked to the progression of the disease is also unknown. Neuronal loss in Parkinson's disease may be caused by oxidative stress inflammation, mitochondrial dysfunction, and abnormalities in protein handling. The cause of development of these psychiatric disorders in PD patients in not clearly understood although the evidence suggests the etiology is multifactorial for all.

4.1. A large number of evidence suggests that the pathophysiological disease process of PD i.e. degeneration of dopaminergic neurons, itself causes some of the causes of depression, cognitive dysfunction, anxiety and apathy seen in people with Parkinson's disease [27]. The deposition of Lewy body in amygdala and para-hippocampus and other brain stem structures is considered central to the development of PDP and sleep disorders[28]. The other factors for depression are depletion of serotonin, and acetylcholine, habenula dysfunction, and impairment at the level of the limbic system, basal ganglia, together with their connections with orbitofrontal cortex contribute to depression. [3,27]

4.2. The anxiety can be attributed to psychosocial, medical, and neurochemical factors. Neurochemically, anxiety in PD may be linked to a loss of dopaminergic and noradrenergic innervation in the locus coeruleus and limbic system [29]. Anxiety disorders in some patients are a 'reactive' response that can be secondary to the PD diagnosis. In others, it may be secondary to the impairment and limitation due to motor symptoms. Anxiety in patients with PD may also be secondary to the anti-parkinsonian medications. (e.g., levodopa, pergolide etc). [8] Discrete anxiety

disturbances at specific times of day (e.g., in late afternoon or early evening) are unique to PD. Such episodes have been found to have an association with fluctuations in levodopa levels and motor function, particularly occurring with the onset of “off” periods. [23] These attacks mostly manifest as panic attacks.

4.3. In PDP dysfunctions in the brainstem's eye movement control mechanisms, subcortical and cortical motion pathways, including dorsal stream areas in the visual parietal lobe are found to have neurobiological association with passage hallucinations. [30]

4.4. The specific dysfunctions implicated for cognitive impairments in PD are reduced dopamine uptake of the frontal lobe, cholinergic disturbance within the brainstem, and cortico-striatal pathways. However, several other neuropathological abnormalities were also reported to have an important role in cognitive dysfunction in PD, such as Lewy bodies and neurites in limbic and cortical regions, amyloid deposition, neurofibrillary tangles, and cerebrovascular disease, mitochondrial dysfunction, inflammation, and abnormalities in levels of neurotrophic factors.

4.5. Apathy can also be correlated to decreased cingulate and inferior frontal gyri volumes. Some studies have suggested apathy as a side effect of Deep Brain Stimulation.

4.6. Poor nocturnal sleep or fragmented sleep can be due to various other PD related symptoms, such as difficulty turning in bed due to rigidity, nocturia, and increased urinary frequency. Poor sleep quality can also be iatrogenic, including drug-induced insomnia caused by dopaminergic or anticholinergic drugs, "off" periods or dyskinesia due to dopaminergic drugs[13]. Other sleep disorders, such as Sleep-disordered breathing (SDB) and RBD, may also contribute to poor sleep quality. Sleep may also be impaired by other psychiatric symptoms such as depression, anxiety and psychosis. Nocturnal sleep disturbances due to any of these reasons, may result in Excessive daytime sleepiness[12,13].

4.7. ICDs were initially reported in PD patients who were on Dopamine agonist (DA) therapies. Some studies report ICDs in the general population and PD patients without DA therapies [31]. It is still under discussion whether PD biology could be a risk factor for ICDs [32]. Classically, impulsivity in PD has been attributed to neuronal dopaminergic degeneration and further manifestations of ICD due to dopamine replacement therapies [33].

5. CLINICAL FEATURES

The clinical features of various psychiatric disorders in PD are:

5.1. **Depression:** The commonly observed symptom profiles included pessimism, hopelessness, decreased motivation, anxiety, suicidal ideation without suicidal behavior, and increased health concern. The patients can present with both dysphoric (irritable) and sad moods [3]. Guilt, self-blame, and worthlessness are uncommon. [5,23].

5.2. **Psychosis:** Symptoms of PDP are mentioned in table 4

Table 4: Symptoms of Parkinson's disease psychosis.

Minor symptoms	These symptoms are not strictly required for the diagnosis but depict PD's early stage and present in increased frequency.
Illusions	A distorted perception of any object. In PD, "Pareidolia" - a specific illusion in which faces and objects are seen in formless visual stimuli, such as clouds, or in geometric visual patterns, such as wallpaper
Presence Hallucinations	A feeling or vivid sensation that someone is nearby
Passage hallucinations	A feeling where a person, animal, or indefinite object is seen passing by
Major symptoms	These symptoms (positive symptoms) are full formed symptoms and depicts a higher stage of PD. E.g., Visual Hallucinations and delusions

The presence of insight indicates early, while absence indicates PD progression along with delusions. Similarly, cognitive deficits along with loss of insight in psychotic symptoms indicate the progressive stage of the disease.

5.3. **Cognitive dysfunction:** The core feature of cognitive dysfunction in PD is executive dysfunction, and patients commonly have difficulty in cognitive flexibility. Problems in memory and attention are particularly prominent. Common symptoms include impairments in executive functioning, processing speed, and spatial working memory. Attention levels may also fluctuate, and the patient may have excessive daytime sleepiness. With the progression, visual hallucinations are common. These are usually animate, unimodal (i.e., affecting only one modality like visual), and generally do not cause dysphoria and fear.

5.4. **Apathy:** changes in personality and mood, particularly depressive and anxiety symptoms, are common.

5.5. **ICDs:** The common manifestations of ICDs in PD include pathological gambling, hypersexuality, compulsive buying/shopping, and binge eating disorders. However, pathological gambling was shifted from the category of ICDs to the category of "Substance-Related and Addictive Disorders" in the DSM-5. The spectrum of ICDs-RD also includes punding, hobbyism, walkabout, hoarding, and compulsive medication use (Dopamine Dysregulation Syndrome or DDS).

6. RISK FACTORS:

The possible risk factors for the common psychiatric disorders in Parkinson disorder patients are enumerated in table 5.

Table 5: The possible risk factors for the various psychiatric disorders in PD patients:

Depression	• Female gender[3,23] • Older-aged PD patients[3] • Personal or familial history of depression[23], • Early-onset PD[23], • "Atypical" parkinsonism (presence of pyramidal symptoms or prominent autonomic signs or rapidly progressive disease)[23], • Psychiatric comorbidity (e.g., impaired cognition, anxiety, psychosis, apathy, fatigue, and insomnia)[23] • Anti-parkinsonian medications[8].
Anxiety symptoms/disorder	• Female gender, • Younger age, • Early onset PD, • More depressive symptoms, • Worse sleep quality, • Severity of PD, • Postural instability, • Gait dysfunction, • Higher rates of motor fluctuations, • Morning dystonia, • Symptom clustering and experience of dyskinesia.[8,34]

Cognitive dysfunction	• Advancing age, • Longer disease duration • Severity of motor symptoms, specifically postural and gait disturbances, • Presence of mild cognitive impairment • Visual hallucinations, Early hallucinations • Male sex, • Smoking, • Alcohol use, • Cardiovascular and cerebrovascular disease • PD patients with poor response to dopamine agonist • Depression
Psychosis	• Older age of onset[35,36] • Longer disease duration • Changes in visual function (diplopia) • Sleep disturbances (rapid eye movement sleep behavior disorder) • Cognitive changes • Dopaminergic medications [24,35] *

Impulse Control Disorders related disorder	• Young age • Male sex • Unmarried[37,38] • Dopaminergic/Dopamine Agonist drugs[33,37] (Pramipexole, Ropinirole, L-dopa, Amantadine, Selegiline) • Monoamine oxidase B inhibitors • Impulse Control Disorders related disorder symptoms prior to PD • Substance abuse • REM-sleep Behavior Disorders (RBD) • Depressive symptoms, anxiety, novelty-seeking[31,33] • Sub Thalamic Nucleus Deep Brain Stimulation * • Personality factors * • Cognitive decline * • Genetic factors (SNPs and FosB overexpression) *

* Controversial supporting data

7. MANAGEMENT:

A. Assessment for psychiatric disorders in PD patients

Table 6: Scales used for assessment of various psychiatric disorders in PD patients.

Disorder	Assessment Scale
Depression in PD	• 15-item Geriatric Depression Scale (GDS-15) * • Hospital Anxiety and Depression Scale (HADS) * • Beck Depression Inventory (BDI)
Anxiety in PD	• Parkinson Anxiety Scale (PAS)* • Beck anxiety inventory (BAI) • Hamilton anxiety rating scale (HARS)

	• Hospital anxiety and depression scale (HADS)
Parkinson's disease psychosis	• Movement Disorder Society United PD Rating Scale (MDS-UPDRS) • North-East Visual Hallucinations Interview (NEVH-I) • Scale for Assessment of Positive Symptoms for PD (SAPS-PD)
Cognitive impairments	• Scales for Outcomes in Parkinson disease–Cognition [SCOPA-COG] * • Montreal Cognitive Assessment (MoCA) • Mini-Mental State Examination (MMSE)
Apathy	• Apathy Scale (AS) • Lille Apathy Rating Scale (LARS)
Sleep disorders	• PD Sleep Scale (PDSS), • Pittsburgh Sleep Quality Index (PSQI), • Scales for Outcomes in Parkinson's Disease Sleep (SCOPA-Sleep) • Epworth sleepiness scale (ESS) • Stanford Sleepiness Scale SSS • Inappropriate Sleep Composite Score ISCS

7.1. **Depression**: Owing to its high prevalence, screening for depression is recommended in PD. There are several validated tools such as the 15-item Geriatric Depression Scale (GDS-15), the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI), along with a clinical interview assessment of depression in PD. The most specific screening tools for depression in PD are the GDS-15 and HADS. These scales are considered more suitable for patients with physical impairments as they remain unaffected by somatic symptoms [3].

7.2. **Anxiety:** Anxiety can be part of the disease process; thus, routine screening is helpful for most patients with PD. This routine screening in PD patients should be done, especially, at the start of the treatment, upon a change in pharmacological treatment and follow-ups. Anxiety can also appear with increasing severity of illness and may be enhanced by motor fluctuations and anti-Parkinsonian drugs.[3] Anxiety in PD can be assessed using several rating scales. Non-specific scales like Beck anxiety inventory

(BAI), Hamilton anxiety rating scale (HARS), and the hospital anxiety and depression scale (HADS) can be useful. Parkinson Anxiety Scale, a PD-specific, validated anxiety rating scale, can be used to assess the severity of anxiety.[39]

7.3. **Psychosis:** Since there was no standard way to diagnose PDP and few specific clinical characteristics of PDP were also reported, in 2007, a joint workgroup from NINDS-NIMH[40] developed diagnostic criteria for PDP [24] (table-7) and the tools used to assess the severity of PDP are mentioned table 6.

Table 7: Diagnostic Criteria for Parkinson's disease psychosis.

PDP (Should meet all three criteria)	PD diagnosis based on the UK brain bank criteria
	≥ 1 PDP symptoms (illusions, false sense of presence /hallucinations /delusions)
	PDP symptoms for ≥ 1 month since PD diagnosis

PD: Parkinson's disease, PDP: Parkinson's disease psychosis

7.4. **Cognitive impairments**: Differentiation of PDD and DLB is often challenging. Although they are believed to be on a Lewy body disease spectrum, some controversy persists in their differentiation in clinical practice. Some researchers even question the need for this differentiation owing to quite similar clinical profile and course of illness, neuro-pathological findings, and treatment approaches. The cluster of clinical signs and symptoms of both DLB and PDD include progressive cognitive impairment associated with Parkinsonism, visual hallucinations, and fluctuations of attention and wakefulness. The major clinical difference between DLB and PDD is the timing of dementia in relation to Parkinsonism. Dementia occurring in the context of well-established idiopathic Parkinson's disease (after at least 1 year of onset of motor symptoms) denotes PDD, and the appearance of earlier cognitive impairment earlier than motor symptoms of Parkinsonism is diagnosed as DLB.

Dementia with Lewy bodies

Patients commonly present with fluctuating cognitive dysfunction with visual hallucinations. Parkinsonian symptoms are also commonly present. Anxiety, depression, and apathy symptoms are usually less prominent than PDD.

Alzheimer's disease

Multiple cognitive domains are affected. Memory, visual-spatial ability, language and executive functions are commonly involved.

Toxic metabolic process

Metabolic dysfunction sometimes presents with the symptoms common in PDD. Clinical features and arterial blood gas analysis, laboratory analysis of blood biochemistry, electroencephalography (EEG), computed tomography (CT) or magnetic resonance imaging (MRI)] etc. may help in diagnosis.

Medication toxicity

Excessive dopamine replacement using medications can cause problems in executive functioning and attention and can also trigger or worsen hallucinations or delusions. Although many medicines can be a potential offender in this regard, dopamine agonists are particularly implicated, and amantadine can cause the above problems in some patients. Carbidopa/levodopa is least troublesome in this regard, but at a sufficiently high dose, carbidopa/levodopa can also aggravate cognitive impairments and precipitate psychosis. Trihexyphenidyl, a central anticholinergic agent used to treat PD tremors, can be particularly detrimental to cognitive functioning.

The common scales used are Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE). A specific scale developed for dementia in PD, Scales for Outcomes in Parkinson disease–Cognition [SCOPA-COG], can also be used.

7.5. **Apathy:** Apathy Scale (AS) [41] is extensively used to screen for and assess the severity of apathy. As the AS is based on subjective evaluation, it has limited use in patients with remarkably low spontaneity. In such patients, Lille Apathy Rating Scale (LARS) [42]can be useful.

7.6. **Sleep disorders:** In patients with PD, the scales used to assess and rate the severity of nocturnal sleep (sleep disturbance & insomnia) and daytime sleepiness are PD Sleep Scale (PDSS), Pittsburgh Sleep Quality Index (PSQI), Scales for Outcomes in Parkinson's Disease Sleep (SCOPA-Sleep), Epworth sleepiness scale (ESS), Stanford Sleepiness Scale SSS and inappropriate Sleep, Composite Score ISCS. These scales are designed to assess severity and to a lesser extent the presence of sleep disturbances. Five out of these six scales (PDSS, PSQI, SCOPA-Sleep, ESS, and ISCS) are designed to have proposed cut off values for the presence of sleep disorder and to discriminate between good and bad sleepers [43].

B. Treatment:

The overall management of PD depends on the status of symptoms, functioning of the patients, impairment, disability, and its impact on quality of life. The medications commonly used for the treatment of PD are listed below (table-8). Common issues and behavioral, affective, and other neuropsychiatric side effects of these medications are also listed [1].

Table 8: Medications commonly used in pharmacological treatment for Parkinson's disease

Medication with class	Dosages	Side effects	Special comments
Dopaminergic Medication			
• Carbidopa/ levodopa	Started at 25/100 TID, dosing titrated as per symptomatic relief.	Dyskinesias more common due to short half-life.	Most potent medication
• Pramipexole	Started at 0.125 mg TID, with gradual building the dose as per clinical response weekly, till a target dose of up to 1.5 to 4.5 mg/daily	Fatigue and drowsiness are noted frequently. May cause compulsive Behaviors.	Less potent than carbidopa/ levodopa. Less potential to cause dyskinesia.
• Ropinirole	Started at 0.25 mg TID with gradual building the dose as per clinical response, up to 24 mg daily doses.		
• Rotigotine	2-mg patch daily, as per clinical response increase weekly, up to 8 mg/day		
COMT and MAO-B inhibitors			
• Entacapone (COMT inhibitor)	200 mg taken with each dose of carbidopa/ levodopa		Prolong the effect of carbidopa/ levodopa and also
• Rasagiline (MAO- B inhibitors)	0.5 mg to 1 mg taken daily.	Potential serotonin syndrome due to multiple drug	

		interaction including serotonergic antidepressants.	increase its side effects.
• Selegiline (MAO- B inhibitors)	5 mg taken daily, if tolerated, increase the dose to 5 mg BID.		
Anticholinergics			
• Benztropine	Started at 0.5 mg BID. Build up the dose based on clinical response up to 2 mg TID.	Dry mouth, dry eyes, urinary retention, cognitive impairments.	Use with caution in elderly.
• Trihexyphenidyl	Started at 2 mg QD. Increase the dose based on clinical response up to 2 mg TID.		

[COMT-Catechol-O-methyl transferase, MAO-B monoamine oxidase aldehyde dehydrogenase B]

Depression: Various guidelines (American Psychiatric Association (APA) CPG, National Institute for Health & Care Excellence (NICE), the Spanish National Health System, and the EFNS/MDS-ES guidelines) have recommended both Selective Serotonin Reuptake Inhibitor (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitor (SNRIs) in the treatment of depression in patients with PD. Among the SSRIs, sertraline is reported as the safest drug. Among the SNRIs, venlafaxine, desvenlafaxine, and duloxetine are considered effective options[3].

However, the SSRI (fluoxetine, sertraline, citalopram, fluvoxamine) may have the potential to exacerbate PD tremors in up to 5% of patients and sometimes worsen parkinsonism[44].

Among the other side effects, few SSRIs appear to increase the risk of pharmacological interactions (Fluvoxamine, fluoxetine, and paroxetine) and dose-dependent cardiac arrhythmia (citalopram and escitalopram)[3,44].

Although efficacious, cautious use of Tricyclic Antidepressants (TCAs) is recommended due to their anticholinergic adverse effects in the PD population. Their use is mainly restricted when there is no response to the second SSRI or SNRI. Nortriptyline and desipramine may be

the safest options considering their lesser risk of anticholinergic effects and therapeutic window than other TCAs [3,44].

A multimodal antidepressant vortioxetine, has high efficacy and tolerability, may be considered a suitable option for PD patients with depression. However, studies assessing the benefits and safety profile of Vortioxetine are not available [3].

Considering the tolerability and efficacy criteria (in the context of absence or a minimal increase in motor symptoms, unlike the SSRIs), other drugs considered useful for depression in PD were bupropion (norepinephrine-dopamine reuptake inhibitor), mirtazapine (noradrenergic and specific serotonergic antidepressant), and tianeptine (glutamatergic modulator). Tianeptine, unlike serotonin-reuptake inhibitor antidepressants, can be safely combined with Parkinson's medication. Bupropion has useful properties like dopaminergic action, lack of serotonergic activity, and subsequent low risk of Parkinsonism, hence it may be useful medicine for PD, but it may also potentially induce psychotic symptoms [3].

There is little evidence on agomelatine and trazodone in this context. Non-ergot Dopamine receptor agonists (pramipexole, ropinirole, and rotigotine) are also considered effective for treating PD-related depression. These agents, however, can magnify the risk of impulse control disorders (ICDs) and thus should be replaced by other options such as antidepressants when patients have no response to 3 mg of pramipexole and 15 mg ropinirole daily [3].

Non-Pharmacological treatment options- The data regarding recommendations of non-pharmacological treatment is insufficient. However, the various options include Electro Convulsive Treatment (ECT), Cognitive Behavior Therapy (CBT), repetitive Trans-Cranial Magnetic Stimulation (rTMS) and Deep Brain Stimulation (DBS).

ECT may alleviate the affective disorder. Delirium is seen in a large proportion of PD patients who have received ECT. However, it can be used for severe, treatment-refractory depression in PD and suicidal or life-threatening affective disorders [3]. ECT can also be used in patients where rapid treatment response is required and the time needed for the treatment response using medications is difficult [8].

The stimulation therapies, e.g., repetitive transcranial magnetic stimulation or rTMS might be useful. The treatment would need to be repeated, as the treatment effect is short-term. [44].

Deep brain stimulation (DBS), especially focused on the subthalamic nucleus (STN), can be considered useful in the short term for managing depressive symptoms. However, with time, the effect can wanes off [8]. Some studies have reported an increased risk of suicide behaviors with the use of DBS in PD [23].

Cognitive behavioral therapy (CBT) is efficacious when symptoms of depression in PD are mild and when antidepressants are contraindicated or undesired [3,23]. According to some studies, caregiver involvement and good executive functioning predict the response of CBT in Parkinson's disease patients [8]. The treatment algorithm for the management of depression in Parkinson's disease is given in table-9, and an overview of the treatment options available for depression in PD is given in table-10.

Table 9: Treatment algorithm for management of depression in Parkinson's disease

STEP 1.	Once the diagnosis of depression is confirmed, review the medications being given for PD management and adjust the doses if necessary.
STEP 2.	If the dose adjustment is not sufficient, treatment according to the severity can be considered. • In mild cases, as the first-line therapy, cognitive behavior therapy or supportive psychotherapy can be considered, if available. However, if psychotherapeutic interventions are not available, pharmacotherapy can be used considering risk-benefit ratio analysis. • In moderate cases, antidepressants or CBT can be considered. SSRIs and SNRIs are the gold standard treatments. Other options include vortioxetine, bupropion, mirtazapine, tianeptine, agomelatine, and non-ergot dopamine agonists such as pramipexole and rotigotine. TCAs such as nortriptyline and desipramine are considered only if there is no response on other available medicines. • In severe and treatment-refractory cases, along with the antidepressant, add on ECT can be considered as an option.

Table 10: Treatment options available for depression in Parkinson's disease.

Medication and its class	Efficacy and practical usefulness	Oher relevant information

• SSRI	Recommended as first line. Sertraline being the safest.	Hold potential to exacerbate PD symptoms (fluoxetine, sertraline, citalopram, fluvoxamine), pharmacological interactions (Fluvoxamine, fluoxetine, and paroxetine), and dose-dependent cardiac arrhythmia (citalopram and escitalopram).
• SNRI	Venlafaxine, desvenlafaxine, and duloxetine are considered safe	
• TCA	Efficacious, considered if no response to the second SSRI or SNRI. Safest options are nortriptyline and desipramine	Used cautiously due to anticholinergic side-effects
• MAO-Inhibitors	No evidence yet	Cautious use with serotonergic antidepressants due to risk of serotonin syndrome
• Other antidepressants (vortioxetine, bupropion, mirtazapine, tianeptine, agomelatine, trazodone)	Given the PD-specific efficacy and tolerability, these can be considered a good option. However, there are no studies available suggesting this.	Bupropion may induce psychotic symptoms
• Non-ergot	May be useful	May increase the risk for impulse control disorder

dopamine receptor agonists (ropinirole, pramipexole, and rotigotine)		
• ECT	Considered useful in severe cases.	Delirium or confusion may be experienced afterward
• rTMS	No sufficient evidence	
• DBS	No sufficient evidence	
• CBT	May be effective	Preferred in mild cases or when antidepressants cannot be given.

Anxiety: There is a lack of conclusive data regarding the various anti-anxiety medications for treating anxiety disorders in people with Parkinson's disease. However, among the various anti-anxiety medications, SSRIs and SNRIs are regarded as the first line of treatment. [8,23] TCAs are better avoided in the elderly.

Anecdotally, benzodiazepines have been noted to be effective in treating anxiety in patients with PD. At high doses, benzodiazepines are associated with a higher risk of falls and subsequent fractures and a higher risk of cognitive impairment in the elderly population and abuse and dependence. These reasons mandate their judicious and careful use along with the lowest possible dose for the minimum possible time in the elderly [8,29]

Anxiety, secondary to various causes, needs to be managed according to the underlying causes. In case of anxiety secondary to anti-parkinsonian medications, it is vital to adjust the dose, and if the anxiety symptoms are not tolerated, replacement of the medication should be considered. Similarly, in patients with panic attacks during off periods, the aim of the treatment should be adjusting the dose of the anti-parkinsonian medication to reduce time off, using FDA-approved medications for motor fluctuations. [8]

Non-pharmacological measures like relaxation, sleep hygiene, social measures for adaptation to PD, and psychoeducation are helpful. CBT techniques that focus on anxiety-provoking maladaptive thoughts and behaviors can effectively treat anxiety attacks and situational anxiety. [45]

PDP: The most important aspect of management of PDP is includes finding out the modifiable risk factors and managing them. Ensuring the functioning of sensory modalities like visual and auditory should be done. Keeping the patient in low stimulations areas with adequate lighting (to avoid minor visual hallucinations), maintaining the circadian rhythm, and reassuring the patients about symptoms are a few important steps. Possibilities of delirium should be ruled out, and the role of drugs having a high propensity of causing delirium should be evaluated. Other causes like dehydration and electrolyte imbalances should be ruled out and managed, if any.

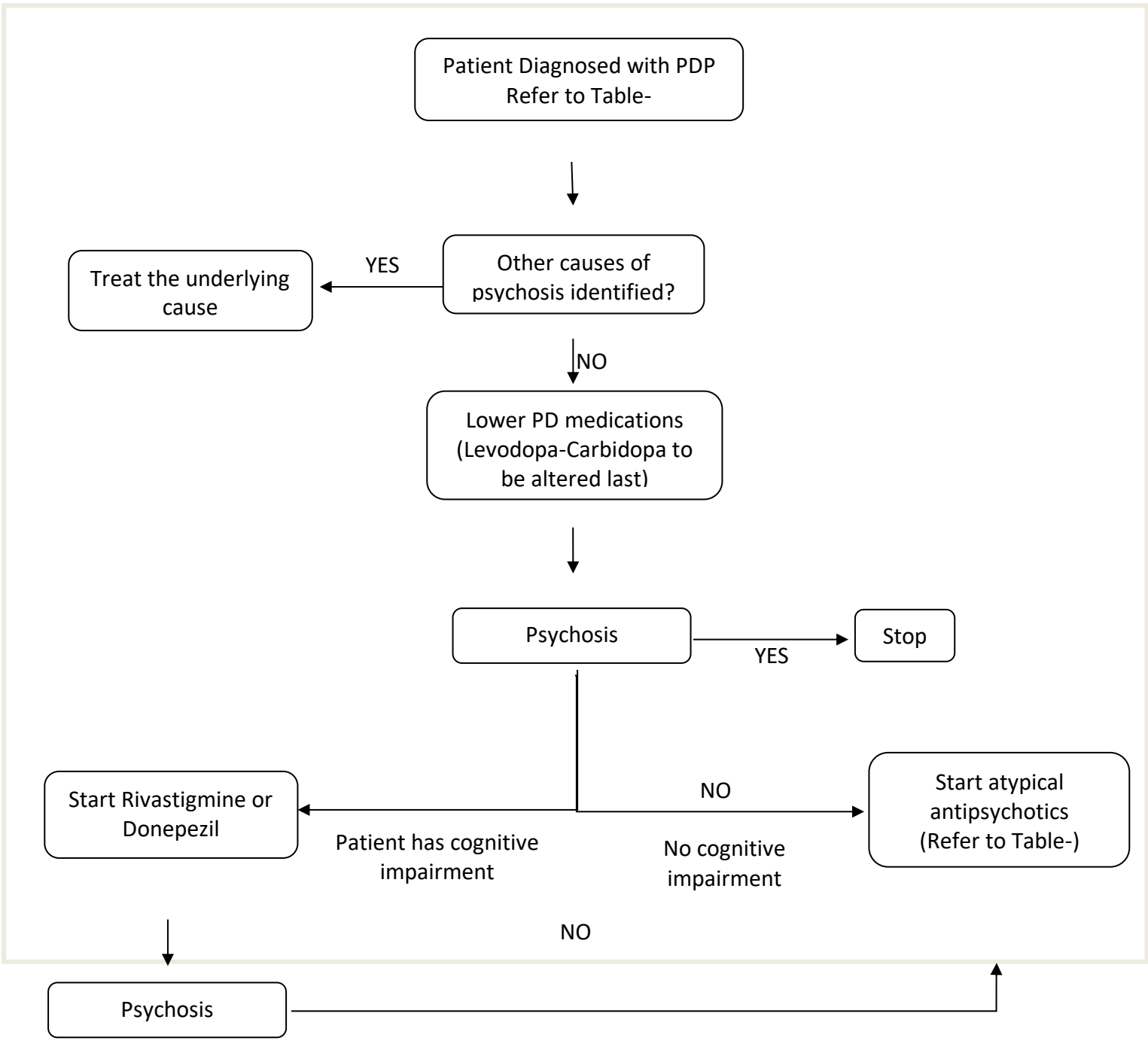
The evidence base for successful pharmacological treatment of PDP is highly lacking. The primary objective of pharmacological treatment is to eliminate polypharmacy and optimum use of essential medications to treat PDP symptoms. Choice of medications should be based on 1) to avoid worsening of motor symptoms and cognitive impairment 2) to decrease the hallucinations. The 2011 Movement Disorder Society, an evidence-based medicine review of treatments, suggests a high risk of worsening motor symptoms with typical antipsychotics as well as few atypical antipsychotics like including olanzapine and risperidone. Among atypical antipsychotics, only clozapine and quetiapine are highly prescribed, but only clozapine has evidence of a needed therapeutic effect on hallucinations. [27] However, the efficacy of quetiapine for treating PDP is unclear, and many studies have shown no benefit with quetiapine treatment. Atypical antipsychotics are advisable for patients with minimal or low cognitive impairment, while in patients with severe cognitive impairments, rivastigmine and donepezil are advisable. [27] [24]

A newer drug pimavanserin received FDA approval in 2016 for PDP treatment (the medicine is not easily available in India as of now) and has shown efficacy without worsening motor or cognitive symptoms. The usual dose is 34 mg once per day. The absorption is not affected by food and there is no need of titration or dosage adjustment for age, sex, weight, ethnicity, or mild to moderate renal failure (CrCL> 30 mL/min). It is not currently recommended for those with severe renal failure (CrCL< 30 mL/min) or hepatic impairment, as it lacks studies in these populations. There is a risk of QTc prolongation with the molecule like atypical antipsychotics, but recently FDA in 2018 mentioned that its benefits are significantly higher than the associated potential risks. As Pimavanserin is metabolized in liver by CYP3A4, hence exposure to potent inhibitors such as ketoconazole should result in dose reduction to 10mg daily. Concomitant use of strong inducers should be monitored as they will reduce the efficacy of pimavanserin [46]. The only limitation suggested in the literature is its cost. (Table-11)

Table 11: Atypical Antipsychotics with doses used in the treatment of Parkinson's disease psychosis

Pimavanserin (FDA approved)	34 mg/d
Clozapine (period blood counts required)	6.25 – 50 mg/d
Quetiapine (unclear efficacy)	50 – 150 mg/d

The algorithm for the management of Parkinson's disease psychosis is depicted in figure-1.



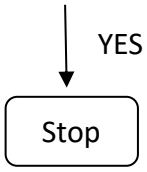


FIGURE 1: The algorithm for the management of Parkinson's disease psychosis.

Cognitive dysfunctions: The treatment for cognitive impairments in PD is still remains poorly researched. As per Food and Drug Administration (FDA), rivastigmine is the only approved treatment for PDD. A mainstay of pharmacological treatment remains the use of cholinesterase inhibitors and memantine. Non-pharmacological treatments are also advocated for use. Cognitive training, both computerized and pen and paper-based methods, are being used. Some studies have suggested improved executive function, working memory, and processing speed in Parkinson's patients and even reduced the risk of developing MCI. Physical exercise in PD can improve motor symptoms as well as ameliorate cognitive dysfunctions also. Exercise interventions like aerobics, resistance training, dance, etc., have been shown to improve neuronal proliferation and neurogenesis. However, large-scale and high-quality clinical trials to further validate the role of non-pharmacological interventions in cognitive impairments in PD are still awaited (Fang et al. 2020). The summary of treatment options is presented in table-12[44].

Currently, evidence-based treatment strategies for milder cognitive impairments are not available. The efficacy of existing medications in halting or slowing rates of cognitive impairments is also not established. The medications that should preferably be avoided in PDD are mentioned in table-13.

Table 12: Medications for Parkinson's Disease Dementia: Summary of evidence.

Medication and its class	Efficacy and practical usefulness	Dosages and administration	Other relevant information
Acetylcholinesterase inhibitors			
• Rivastigmine	Efficacious, practically useful	Start with 1.5 mg BD, increase by 1.5 mg every 2-4	Approved by Food and Drug Administration for

		weeks. Maximum dose is 6 mg BD, PO Transdermal 4.6 mg/d X 4 weeks, may be increased up to 9.5 mg/d	Parkinson's Disease Dementia
• Donepezil	Insufficient evidence, potentially useful	5 mg/d, can be increase up to 10 mg/d after 4 weeks	
• Galantamine	Insufficient evidence, potentially useful	4 mg BD, can be increased to 8 mg/d after 4 weeks, maximum dose 12 mg/d	
N-methyl-D-aspartate (NMDA) antagonists			
• Memantine	Insufficient evidence, potentially useful	Start with 5 mg/d, can be increased 5mg after one week, the maximum dose is 10mg BD	
Monoamine oxidase B (MAO-B) inhibitors			
• Rasagiline	Insufficient evidence, investigational	Monotherapy- 1 mg/day With levodopa- 0.5mg/day	Risk of hypertension
Selective norepinephrine reuptake inhibitors			
• Atomoxetine	Insufficient evidence, investigational	Start from 40 mg, usual dosages are 80 mg in adults	

Non-pharmacological Interventions			
• Transcranial direct-current stimulation (t-DCS)	Insufficient evidence, investigational	NA	
• Cognitive rehabilitation	Insufficient evidence, investigational	NA	

Table 13: Medications preferably avoided in Parkinson's Disease Dementia.

Dopamine antagonist (D2 receptor) Both typical (Haloperidol, trifluoperazine, etc.) and atypical antipsychotics with high affinity for D2 receptors (Risperidone, olanzapine, etc.)	It can cause drug-induced parkinsonism, may exacerbate executive dysfunction and inattention, somnolence, postural hypotension, May cause neuroleptic malignant syndrome, risk of increased mortality in dementia patients
Anticholinergic medications Both central anticholinergic medications (benztropine and trihexyphenidyl)	Increases risk of cognitive dysfunctions

Apathy: There are no proven medicines for apathy. However, due to its pathophysiological association with dopamine deficiency, the effectiveness of few dopaminergic agents has been suggested. Pramipexole, a dopamine agonist, is reported to cause improvement in the symptoms of decreased willingness in apathy. Amantadine hydrochloride enhances dopamine secretion and stimulates a catecholamine action. Hence can be useful in apathy. [10]

A cholinesterase inhibitor (rivastigmine) also has positive RCT results, suggesting its possible use to treat PD apathy [44]. In addition to these agents, stimulant-like (methylphenidate) and stimulant (amphetamines) medications are used clinically, and the structurally antidepressant to these stimulants, bupropion, can also be used in the treatment of PD-Apathy[23].

Sleep disorders: Common points in the management of sleep disorders in PD-

- Establishing the cause that involves reviewing the patient's medications, sleep hygiene and comorbid conditions.

- The patient should be advised to maintain a sleep log, including various problems encountered during sleep.
- A detailed neurologic and general medical history and examination should be carried out.

The treat approach for different sleep disorders in PD are different as mentioned below.

INSOMNIA IN PD-

The initial step is to treat the motor symptoms optimally, which are considered a major cause of physical discomfort during nocturnal sleep. For this, low doses of dopamine receptor agonists in the evenings can be considered and the judicious use of slow-release preparations is also useful.

Before starting pharmacological therapy for insomnia, sleep hygiene, relaxation techniques, and cognitive behavior therapy should be considered.

Pharmacotherapy- earlier used benzodiazepines have almost been replaced by zopiclone and eszopiclone for the management of insomnia. The effective dose in the elderly is considered to be 3.75 mg, which can be increased up to 5 or 7.5mg may be needed [47]. Doxepin has also been proven in patients of PD with insomnia [48]. Melatonin can be considered in patients who have not shown benefits from the newer hypnotics and doxepin [49].

EXCESSIVE DAYTIME SLEEPINESS (EDS)-

Identifying and managing comorbidities (underlying depression, fatigue, disruption in night sleep, and OSA) is the mainstay of managing EDS in patients with PD.

Another useful step in patients with EDS is D2-receptor agonists titration to the lowest possible dose or complete discontinuation of these agents.

Pharmacotherapy- modafinil, caffeine, and atomoxetine can be considered an effective treatment in EDS, but the result regarding their use is conflicting [50].

RAPID EYE MOVEMENT SLEEP BEHAVIOR DISORDER (RBD) IN PATIENTS WITH PD-

In patients diagnosed with RBD, SSRIs, SNRIs, TCAs such as clomipramine, and beta-blockers such as bisoprolol should be discontinued as they can cause RBD secondary to their use.

Pharmacological- melatonin and clonazepam. Out of which, melatonin is regarded as a good alternative (gradually increasing the dose up to 12 mg/night)[51].

RESTLESS LEGS SYNDROME-

RLS can be secondary to various disorders such as iron deficiency anemia, peripheral neuropathy, myelopathy, diabetes, and uremia because of renal insufficiency. The initial steps in the management of RLS is identification and evaluation of these secondary causes.

The α2δ ligands (gabapentin & pregabalin) is considered as the first-line agents for the treatment of RLS [51]. The other option is dopaminergic medications such as pramipexole, rotigotine, ropinirole and levodopa. However, their side effects such as pedal edema, impulsive behavior disorders, EDS, and the morning rebound phenomenon are less preferred nowadays [52]. The studies give mixed results for Botulinum neurotoxin (BoNT) in RLS treatment.

OBSTRUCTIVE SLEEP APNEA IN PATIENTS WITH PD-

Patients with RBD have higher risk of OSA, thus RBD should be ruled out. In the case of obese patients, weight reduction is strongly advised. In severe cases of OSA, the mainstay of therapy remains the continuous positive airway pressure (CPAP), this leads to significant improvement in quality of sleep. In the patients not compliant to CPAP therapy sustained release formulations of levodopa before sleep can be considered an option though any specific guidelines for the dose titration are not available.[13]

ICD: The primary approach for ICD is prevention and psychoeducation of patients and family members regarding the potential risks of different dopaminergic medications. Before starting Dopaminergic medications, one should assess the cost-benefit of predisposing risk factors (Table-16) and the prescribed drugs. Apart from genetic factors, the treatment decision must consider clinical findings, such as younger age, early onset of PD, longer duration of illness (PD), personal history of addictive behaviors, male gender, short-acting DA drugs, behavior, mood disorders (depression), DBS and certain cultural factors. It is also important to inform patient/family members about the Dopaminergic treatment and its impact on their care giving and life. The NICE guideline suggests taking informed consent before starting DA medications[53].

When ICDs appear, treatment continues to be a challenge, and it must be tailor-made according to the patient's clinical factors, such as the severity of motor symptoms, comorbidities, and quality of life[33,54]. The first step for the treatment of ICDs is either reduction or discontinuation of DAs. However, it should be kept in mind that neuropsychiatric symptoms may persist for at least 12 weeks after drug discontinuation. Nonetheless, in certain cases still have the risk of

developing DA withdrawal syndrome and worsening motor symptoms[33,55]. There is controversial evidence regarding use of SSRI's, atypical antipsychotics and opioid antagonists in cases of ICDs.

Several drugs were reported to be potentially efficacious in increasing GABAergic inhibition (valproate, topiramate) and new drugs to preserve the ventral striatal DA system (zonisamide, donepezil), noradrenaline reuptake inhibitor) and can be useful in the treatment of ICDs. [53].

As previously mentioned, data concerning DBS and ICD treatment is still controversial. DBS may lead to a reduction in dopaminergic requirements hence may be efficacious. It has been suggested that STN stimulation could reduce the risk for Impulse Control Disorders by increased reward-driven behaviors by inhibitor effect in the indirect dopaminergic pathway. However, some patients may develop transient de novo ICDs after STN DBS, and selective patients may develop ICDs a long time after DBS [33,53].

Non-pharmacologic approaches can be effective, including cognitive behavioral therapy and patient and caregiver education [53]. Table 14 gives a brief overview of the Management approach for ICDs-RD in PD.

Table 14: Management approach for Impulse Control Disorders related disorder in PD.

Address modifiable risk factors (Table-)	Lower dopaminergic drugs Switch DA drugs
Manage comorbidities	E.g., SSRIs for depressive and anxiety symptoms
Non-pharmacologic approach	CBT Patient and caregiver education
Pharmacological management (Limited evidence)	Valproate, Topiramate Clozapine, Quetiapine Naltrexone, Nalmefene Zonisamide, Donepezil, Noradrenaline reuptake inhibitor SSRIs

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Management of psychiatric disorders in patients of epilepsy

Dr. Jahnavi Kedare, Dr. Sachin Baliga

Introduction

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) defined an epileptic seizure in 2005 as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. It is a disorder of the brain that results in a predisposition to induce seizures and to its neurobiological, cognitive, psychological, and social consequences. In 2014, International League Against Epilepsy gave an operational definition of epilepsy which requires two unprovoked seizures separated by more than 24 hours, or One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years or diagnosis of an epilepsy syndrome.

Epilepsy is a common neurological disorder. It is seen in nearly 70 million people worldwide. 90% of cases of epilepsy belong to developing countries. The prevalence rate in India varies from 1.2 to 11.9/1000 among adult population.

Psychiatric disorders occur very often in patients with epilepsy. A comorbidity with epilepsy is a condition that occurs along with epilepsy. It may pre-exist even before the onset of epilepsy, may be the cause or the consequence of epilepsy and may occur any time during the course of the disorder. Psychiatric disorders commonly seen in epilepsy include depression, anxiety disorders, psychosis, personality change, cognitive abnormalities and attention deficits.

Psychiatric disorders go unnoticed in these patients as control of seizures becomes the focus of management and many times clinicians are not aware that psychiatric disorders may occur in patients with epilepsy. It is important to diagnose and treat psychiatric disorders as they cause poor response to treatment, affect the quality of life of the patient and increase the risk of early death due to suicide or accidents.

Prevalence of psychiatric disorders in patients with epilepsy is much higher than in general population. Various population studies have reported prevalence of psychiatric disorders ranging from 5.9% to 54.9%, maximum being 80% in some patients of temporal lobe epilepsy. In two Indian studies prevalence of psychiatric disorders was found to be higher than in patients with other chronic illnesses like asthma and healthy controls.

The percentage of epilepsy patients in psychiatric hospitals was also higher than the prevalence of
epilepsy in the community. It ranged from 4.7 percent amongst inpatients in a British psychiatric hospital to 9.7 percent in a US Veterans Affairs psychiatric hospital.

Approximately 30% of patients attending epilepsy clinics had a past history of psychiatric hospitalization and 10-20% were on some psychiatric medication.

Etiology and risk factors for developing psychiatric disorders in epilepsy can be summarized as follows.

Table 1: Etiology and risk factors for developing psychiatric disorders

Risk factors for psychiatric disorders in epilepsy	
Biological	Type of epilepsy, Severity of epilepsy, Ictal and interictal neuronal activity, Disturbances in sleep wake schedule, Traumatic brain injury
Psychosocial	Stigma, constrains in lifestyle, low self esteem, limitations in vocations and educational achievement, Dependence on others for socioeconomic needs, poor social support
Treatment related	Poor adherence to treatment, polytherapy, Side effects of antiepileptic medication.

Bidirectional Hypothesis:

Various epidemiological studies suggest that the relationship between epilepsy and psychiatric disorders is bidirectional. Depression, anxiety disorders and psychotic disorders do not occur only secondary to epilepsy but can also precede epilepsy indicating that there may be some common psychopathology involved. In depression the proposed common pathophysiological changes are seen in hyperactivity of hypothalamic-pituitary- adrenal axis and changes in glutamate and GABA. Structural changes in the form of decreased volume of hippocampus and frontal lobes is seen both in depression and epilepsy. Psychotic disorders share a common pathophysiology with epilepsy in the form of a dopamine overactivity in mesial temporal regions and limbic system along with a decreased dopamine activity in ventrolateral and dorsolateral prefrontal cortices.

Depression:
A meta-analysis by A.J. Scott in 2017 gave pooled prevalence of depressive disorders in epilepsy as 22.9%. The Canadian Community Health Survey (CCHS) conducted in 36984 people described the prevalence of major depressive disorders as 17.4% and EPIC study from US gave a prevalence of 32.5%. Disability due to epilepsy, stigma experienced by persons with epilepsy(PWE), poor social support act as risk factors for developing depression. PET studies have demonstrated deficits in 5HT1A receptor binding in medial temporal regions seen both in depression and temporal lobe epilepsy. Some of the neuronal networks in the frontal and temporal regions may be involved both in causation of frontal and temporal epilepsy and dysregulation of mood and behaviour. Depression adversely affects the course of the illness in epilepsy. It leads to poorer quality of life, poorer response to treatment, poorer results after surgery.

Psychosis:

Prevalence of psychosis in epilepsy ranges from 7 to 12%. The risk of psychosis increases 5 to 8 times in patients with epilepsy as compared to that in general population. 7% patients of temporal lobe epilepsy develop psychotic disorders as against 5.6% in other types of epilepsy.
Risk factors for developing psychotic disorders are

1) Sever cases of epilepsy
2) Family history of epilepsy and family history of schizophrenia
3) Temporal lobe epilepsy, especially with history of febrile seizures
4) Hippocampal sclerosis on MRI
5) Presence of autoantibodies anti NMDA, anti GABA-B receptor, anti voltage gated potassium channel(VGKC) (seen in 10% patients)

Psychosis can occur as ictal, postictal and interictal phenomenon. A phenomenon of 'forced normalization' has been described in patients in whom psychotic episode emerges when seizures seem to be under control. A chronic schizophrenia like psychosis is also seen.

Anxiety disorders:
A meta-analysis by A.J. Scott in 2017 gave pooled prevalence of anxiety disorders in epilepsy as 20.2%. EPIC study from US gave a prevalence of 22.4%. Anxiety disorders in patients with epilepsy go unnoticed because of number of reasons. Anxiety disorders coexist with depression very often. Many a times a panic attack is mistaken for ictal fear. Sometimes they are considered as a natural emotional reaction to having a diagnosis of epilepsy and a consequence of functional limitations caused by it. Panic disorder, generalised anxiety disorder, agoraphobia, social phobia and rarely obsessive compulsive disorder are seen in patients with epilepsy. While diagnosing these anxiety disorders thyroid and other endocrine abnormalities and medication side effects need to be ruled out.

Ictal, postictal and interictal psychiatric disorders:

Behavioural disturbances and psychiatric syndromes occur during ictal, peri-ictal, postictal and interictal period. They have characteristic features. They need to be identified and treated along with the seizure disorder. The following table gives a summary of such psychiatric syndromes.

Table 2: Ictal, Peri-ictal, Postictal and Interictal Psychiatric disorders

	Depression	Anxiety	Psychosis
Ictal	Less common than anxiety disorders, present with guilt, hopelessness, worthlessness, and suicidal ideation.	Fear as a part of aura, one-third of patients of partial seizures involving right temporal foci.	Associated with partial seizures. Present with ill-defined visual, gustatory or auditory hallucinations
Postictal	May last for 2 weeks. May range from mild to severe associated with suicidal ideas. More common in right	Seen less commonly than depression.	Occurs after a cluster of complex partial seizures (+/- secondary generalisation). Onset of psychosis is after 12-72 hours of lucid interval.

	temporal and frontal foci.		Presents with delusions, hallucinations, thought disorder or mania. Transient in nature, but may last for several weeks. May be recurrent.
Interictal	Seen in drug resistant epilepsy, TLE with hippocampal sclerosis, hypoperfusion of bifrontal and temporal regions, Stigma, dissatisfaction with life also seen . Present with persistent low mood, anhedonia, loss of interest and sleep or appetite disturbances.	Associated with left sided temporal lobe epilepsy. Stigma, functional difficulties may cause anxiety.	Chronic schizophrenia like disorder. Onset is after more than 10 years of epilepsy. More often in patients with an early age of onset, poor response to treatment and bitemporal foci, more with left sided foci.

Evaluation and assessment

A detailed evaluation for psychiatric disorders in epilepsy includes the following :

Table 3: Evaluation and Assessment

Clinical history of epilepsy	Age at onset, clinical features including impairment in consciousness, nature of seizures, generalized/focal, type of seizure
Clinical history of psychiatric disorders	History suggestive of depression, anxiety, psychosis, attention deficit disorder, cognitive impairment, suicidality, aggression. Relationship to seizures e.g. postictal, ictal, interictal
Past and family history	Psychiatric disorders, Epilepsy
Impact of illness	Patient's understanding of the nature of the illness, their concerns, functional difficulties, perceived social support and stigma
Treatment history	Epilepsy, Psychiatric disorders- Response, side effects
Assessment of caregivers	Caregiver burden, understanding of the nature of the illness, their concerns, social support and stigma.
Clinical examination	Neurological examination, Mental status examination
Investigations	EEG, video EEG, MRI, CT scan.
Psychometric tests	Rating scales, Cognitive tests

A variety of psychometric scales and tests have been used to assess, quantify and monitor psychiatric issues in epilepsy and have been specifically validated for use in this population. The following table lists the same and also mentions whether these are available freely in public domain or require to be purchased. Since the status of availability can change from time to time, it is recommended to check the latest updates online before using them.

Table 4: Scales for assessment of psychiatric disorders in epilepsy

Disorder/ Domain	Validated tools	Availability
Depression	Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) Patient Health Questionnaire-9 (PHQ-9) Beck Depression Inventory-II Hospital Anxiety and Depression Scale (HADS) Major Depression Inventory (MDI)	Free Free Paid Paid Paid
Anxiety	Generalized Anxiety Disorder-7 (GAD-7) Hospital Anxiety and Depression Scale for anxiety (HADS-A)	Free Paid
Personality Disorders	Bear-Fedio Inventory (BFI) Minnesota Multiphasic Personality Inventory-2 (MMPI-2)	Paid Paid
Aggression	Buss-Durkee Hostility Inventory (BDHI) Aggression Questionnaire (AQ)	Paid Paid
Suicidality	Item 4 of the NDDI-E Item 9 of the PHQ-9 Mini-International Neuropsychiatric Interview (MINI) Suicidality module	Free Free Paid
Cognitive deficits	Montreal Cognitive Assessment (MoCA) Mini–Mental State Examination (MMSE) Wechsler Adult Intelligence Scale (WAIS) and Wechsler Intelligence Scale for Children (WISC)	Free Paid Paid

Management of psychiatric disorders in epilepsy

1. **Pharmacotherapy**

There is a paucity of data on treatment of psychiatric issues in epilepsy patients due to lack of systematic studies. Existing guidelines rely heavily on data from clinical experience and open-label studies and generally recommend following similar treatment considerations as those in non-epilepsy individuals. However, there are certain principles of pharmacological management which the clinicians need to know while prescribing psychotropic medications in patients with epilepsy.

A) ***Principles of pharmacotherapy***:

Pharmacokinetic interactions:

The older AEDs such as carbamazepine (CPZ), phenytoin and barbiturates (PB) are potent inducers of several cytochrome P450 (CYP) and UDP-glucuronosyltransferase (UGT) enzymes. On the contrary, Valproate (VPA) is a broad-spectrum enzyme inhibitor on the CYP and UGT enzymes. As a result, pharmacokinetic interactions with a lot of antidepressants, antipsychotics and other psychotropic agents are expected. Newer AEDs have a better profile with a low risk of pharmacokinetic interactions. Particularly, Oxcarbazepine (OXC) and topiramate (TPM) may have weak inducing properties, especially at high doses.

Among antidepressants, a reduction in plasma levels of SSRIs (by at least 25%), mirtazapine, venlafaxine and bupropion (up to 90%)is seen. Interactions between older AEDs and TCAs are generally not clinically relevant. VPA has been seen to slightly increase plasma levels of O-desmethylvenlafaxine, the active metabolite of venlafaxine, but does not cause interactions with other antidepressants. Similarly, CBZ reduces plasma levels of all typical antipsychotics. Among atypical antipsychotics, plasma reduction has been noted for aripiprazole, clozapine, olanzapine, paliperidone, quetiapine (can reduce to undetectable levels), risperidone and ziprasidone. Interactions between VPA and antipsychotics are generally not clinically relevant and may be considered only on an individual basis.

Pharmacodynamic interactions

Pharmacodynamic interactions can be of both positive and negative varieties. For example, interactions between AEDs and SGAs are well known and are commonly utilized in management of mania. The negative ones are more commonly known due to their propensity to cause side effects. In general, negative pharmacodynamic interactions between antipsychotics and AEDs that can be clinically relevant include increased sedation, weight gain and hematologic side effects.

Psychotropics and seizure threshold table

When it comes to drug-related seizures, the risk of seizure induction is generally associated with a higher-dose or overdose, rapid up-titration, abrupt withdrawal (for example, BZDs), pharmacokinetic effects (enzyme inhibition leading to increased levels) or pharmacodynamic effects on seizure threshold. These particularly hold true for in patients with epilepsy and those with co-existing neurological disorder (brain trauma, dementia). Among antidepressants, high dose of clomipramine and amitriptyline (>200mg), maprotiline and high dose bupropion immediate release formulation (>450 mg) seem to be more frequently associated with seizures than others.

Antipsychotics, in general have low proconvulsant risk. Clozapine is the only antipsychotic which has shown both titration-dependent and dose-dependent risk of inducing seizures. Studies have shown prevalence rates of around 1, 2.7, and 4.4% for dosages of < 300 mg, 300–600 mg, and > 600 mg, respectively. Clozapine, as well as olanzapine have also been noted to induce EEG changes such as epileptiform activity or generalized slowing. However, the association between olanzapine and clinical seizures is less consistent. Other antipsychotics are considered safe in individuals with epilepsy.

Table 5:

Psychotropics associated with reduction in seizure threshold
Antidepressants High risk: TCAs (high doses >200mg), bupropion (>450mg), maprotiline Moderate risk: Trazodone, vilazodone, venlafaxine Low risk: SSRIs, mirtazapine
Antipsychotics:

High risk: Clozapine, chlorpromazine, loxapine, zotepine Moderate risk: Olanzapine Low risk: Aripiprazole, risperidone, amisulpride, ziprasidone, haloperidol, trifluperazine, flupenthixol, fluphenazine

Effect of antiepileptics on psychiatric symptoms table

AEDs such as valproate, carbamazepine and lamotrigine are also established mood stabilizers and are commonly used in treatment of psychiatric disorders. However, certain AEDs have also been reported to cause worsening or even de-novo development of psychiatric symptoms, termed as psychiatric and behavioural side effects or PBSEs. Those with absent seizures, secondary generalized seizures and those with intractable epilepsy (poor seizures control on two or more AEDs) are particularly noted to have a higher risk of PBSEs. Levetiracetam has been noted to be associated with the highest incidences of aggression, mood and psychotic disorders. Similarly, Zonisamide has also been associated with incidences of depression, psychosis and aggression. Particularly in those with a history of previous psychiatric illness, one should keep a watch for resurgence of symptoms. In case of development of recent onset psychiatric symptoms in patients on these AEDs in those without a history, the possibility of it being treatment-emergent should be considered by the clinicians.

Table 6: Psychiatric and behavioural side effects (PBSEs) due to antiepileptic drugs

High risk: Levetiracetam, zonisamide Low risk: carbamazepine, oxcarbazepine, phenytoin, valproate, clobazam, gabapentin, lamotrigine Uncertain risk: Tiagabine, topiramate

Table 7: Dosages of commonly used drugs for treatment of psychiatric issues in epilepsy:

Name	Usual adult dose range
Antidepressants	
Tricyclic antidepressants (TCAs)	
Amitriptyline	100-200mg
Nortriptyline	50-200mg
Selective serotonin reuptake inhibitors (SSRIs)	20-60mg
Citalopram	5-30mg
Escitalopram	10-80mg
Fluoxetine	100-300mg
Fluvoxamine	25-200mg
Sertraline	10-60mg
Paroxetine	
Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)	75-375mg

Venlafaxine Norepinephrine and specific serotoninergic antidepressants (NaSSAs) Mirtazapine Norepinephrine and dopamine reuptake blockers (NDRIs) Bupropion	 15-60mg 150-450mg
Antipsychotics First generation antipsychotics (FGAs) Haloperidol Trifluoperazine Chlorpromazine Second generation antipsychotics (SGAs) Olanzapine Risperidone Quetiapine Lurasidone Amisulpride Aripiprazole Ziprasidone	 2-20mg 10-30mg 200-1000mg 5-20mg 2-16mg 150-800mg 40-160mg 300-1200mg 10-30mg 40-160mg

Table 8: Drug interactions

Drug class	Examples	Drug interactions with AEDs
Antidepressants Tricyclic antidepressants (TCAs)	Amitriptyline, imipramine, clomipramine, nortriptyline, maprotiline	Pharmacokinetic interactions with inducers (generally not clinically relevant). Increased risk of seizures with high doses (>200mg)
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine	Pharmacokinetic interactions with inducers
Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine, duloxetine, desvenlafaxine, milnacipran	Pharmacokinetic interactions with inducers
Norepinephrine and specific serotoninergic antidepressants	Mirtazapine	Pharmacokinetic interactions with inducers

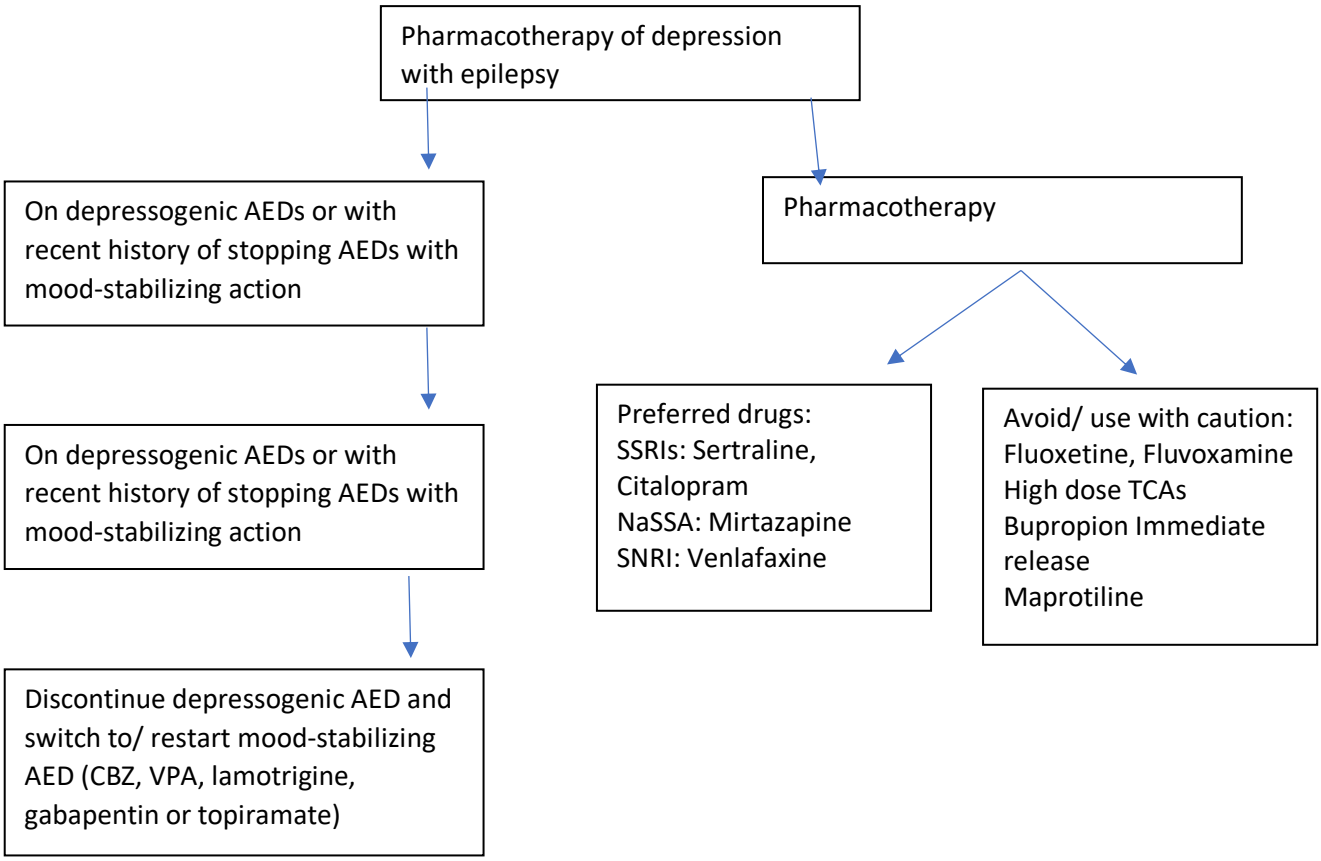
(NaSSAs) Norepinephrine and dopamine reuptake blockers (NDRIs)	Bupropion	Pharmacokinetic interactions with inducers. Increased risk of seizures with high doses of immediate release formulation (>450mg)
Antipsychotics First generation antipsychotics (FGAs) Second generation antipsychotics (SGAs)	Chlorpromazine, fluphenazine, haloperidol, pimozide, thioridazine, trifluoperazine Olanzapine, risperidone, amisulpride, quetiapine, aripiprazole, ziprasidone, asenapine, paliperidone, clozapine	Pharmacokinetic interactions with inducers. Pharmacokinetic interactions with inducers. Increased risk of seizures with clozapine.
Psychostimulants	Methyphenidate, atomoxetine, dexamphetamine	Pharmacokinetic interactions with inducers (methyphenidate)

Table 9: Side effects of medications

Drug class	Examples	Side effects
Antidepressants Tricyclic antidepressants (TCAs)	Amitriptyline, imipramine, clomipramine, nortriptyline, maprolitine	Increased risk of sedation, weight gain, sexual dysfunction, urinary retention
Selective serotonin reuptake inhibitors (SSRIs)	Citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine	Increased risk of hyponatremia, sexual dysfunction, weight gain (especially citalopram)
Dual serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine, duloxetine, desvenlafaxine, milnacipran	No specific pharmacodynamic interactions
Norepinephrine and specific serotoninergic antidepressants (NaSSAs)	Mirtazapine	Increased risk of weight gain and sedation
Norepinephrine and dopamine reuptake blockers (NDRIs)	Bupropion	Increased risk of seizures for dosages > 450 mg for immediate release formulation

Antipsychotics First generation antipsychotics (FGAs)	Chlorpromazine, fluphenazine, haloperidol, pimozide, thioridazine, trifluoperazine	Increased risk of sedation and weight gain
Second generation antipsychotics (SGAs)	Olanzapine, risperidone, amisulpride, quetiapine, aripiprazole, ziprasidone, asenapine, paliperidone, clozapine	Increased risk of sedation and weight gain (particularly olanzapine) Increased risk of seizures (Clozapine) Increased risk of agranulocytosis (Clozapine with CBZ)

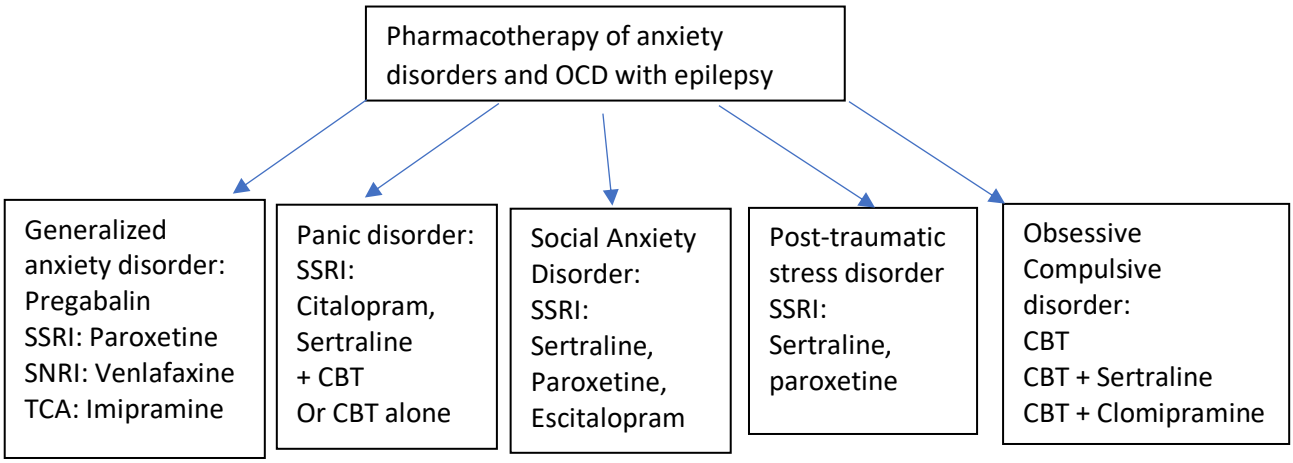
Pharmacological management of mood and anxiety disorders



The primary goal of treatment of depression should always be complete remission of symptoms. Clinicians should also keep in mind the other possible side effects due to pharmacodynamic interactions between antidepressants and AEDs such as hyponatremia, sedation, weight gain, sexual dysfunction etc.

For treatment of manic episodes or bipolar depression in PWE, AEDs such as CBZ, VPA, lamotrigine, gabapentin and topiramate should be regarded as first choice drugs. Administration of lithium in epileptics has a secondary place because of its known association with encephalopathy especially when used in combination with CBZ. Lithium is also considered proconvulsant due to its tendency to induce EEG abnormalities. However, it can be a second-line alternative treatment and may prove useful when part of an augmentation strategy.

In case of severe depression presenting with suicidality or treatment resistance, as well as in manic episodes, electroconvulsive therapy (ECT) is not contraindicated and should be considered as an important treatment modality. However, clinicians have to be aware of potential ECT related issues such as high seizure threshold due to co-administration of AEDs and risk of prolonged or tardive seizures. Subsequently, a higher strength of electrical stimulus as well as close monitoring of seizure duration may be required. Importantly, ECTs are known to increase convulsive threshold over a period of time, which could prove beneficial for managing epilepsy.



For management of anxiety disorders such as panic disorder, social anxiety disorder and post-traumatic stress disorder, SSRIs are considered as the first line. Due to its synergistic effects, Pregabalin could also be considered as the first line when both epilepsy and generalized anxiety disorder co-exist simultaneously.

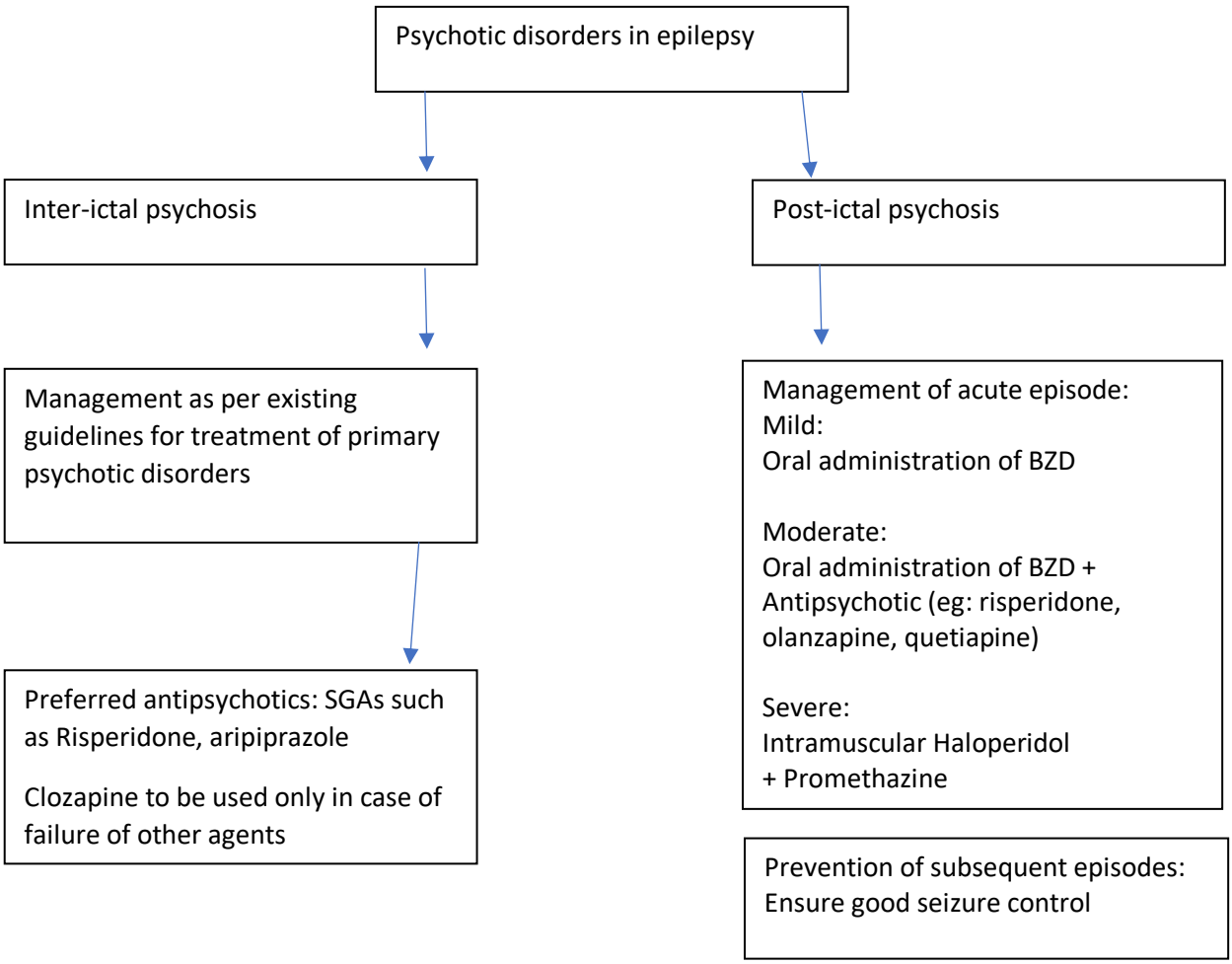
With regards to duration of treatment, it is recommended that clinicians follow guidelines of treatment of mood and anxiety disorders outside of epilepsy.

The recommendations for treatment of anxiety disorders in PWE have been summarized in table.

Table 10: Recommendation for management of anxiety disorders

Panic disorder	SSRI (Sertraline, Citalopram) + CBT or CBT alone
Generalized anxiety disorder	1. Pregabalin 2. Paroxetine, Venlafaxine, Imipramine
Social anxiety disorder	SSRI (Sertraline, Paroxetine, Escitalopram)
Post-traumatic stress disorder	SSRI (Sertraline, Paroxetine)
Obsessive compulsive disorder	1. CBT 2. CBT + Sertraline 3. CBT + Clomipramine

Pharmacological management of psychosis in epilepsy



Due to lack of direct studies, it is recommended that clinicians follow guidelines of treatment of psychosis outside of epilepsy. However, using lowest possible therapeutic dose and careful clinical monitoring is recommended. Second generation antipsychotics (SGAs) such as risperidone and aripiprazole are preferred due to their favorable profile with respect to acute extra-pyramidal side-effects as well as better long-term tolerability. Clozapine should only be used when other antipsychotics have failed to show improvement. Furthermore, low starting doses, low titration rates, and careful clinical monitoring are additionally recommended. Long-

acting formulations of antipsychotics are not recommended since it is difficult to discontinue the causative drug immediately in case of seizures.

Due to lack of sufficient data, psychotic symptoms in inter-ictal psychosis are generally treated in line with treatment protocols for schizophrenia and related psychotic disorders. Based on existing literature, a continuous antipsychotic treatment for at least 1 year is recommended in patients with first-episode psychosis, while in patients with previous history of multiple episodes, treatment should be maintained for 2–5 years. Indefinite continuation is recommended in those with a history of suicide attempts or violent and aggressive behaviour or very frequent relapses.

Treatment of post-ictal psychosis involves a two-pronged approach of managing acute episode and prevention of repeat episodes. Acute episodes, especially in the initial period can be terminated by oral administration of a BZD. However, non-response to a BZD and progressive symptoms warrants oral administration of a BZD and an antipsychotic (for example; risperidone, quetiapine, olanzapine) in combination. Clinicians should also keep in mind the possibility of a paradoxical response with BZD. In individuals with severe agitation and those with a history of violence during past episodes, intramuscular administration of antipsychotic such as haloperidol with promethazine is recommended.

In most cases, symptoms of post-ictal psychosis subside within a week. Sedatives should be reduced gradually and can be tapered completely on average within 1 - 3 months of the last episode. Ensuring good seizure control prevents recurrence of further episodes. Hence, continuous administration of antipsychotics is not recommended.

2. Psychosocial interventions

Psychosocial management forms an important part of management of psychiatric issues in PWE. The following table summarizes the various psychological issues pertaining to PWE along with the psychosocial approaches for addressing them. Only those that have shown significant benefits in studies have been enlisted.

Table 11: Psychosocial interventions

Domain	Psychosocial intervention
Depressive symptoms	Skill-based training and behavioral interventions: Techniques focusing on behavioral and social activation, problem solving and goal setting skills, training of social competencies, and identifying social support
Anxiety symptoms	Mindfulness based interventions CBT
Social problems and stigma	Addressing internal factors contributing to social problems and stigma such as social and communication skills (eg, assertion training, training of epilepsy-related communication),

	social activation (eg, community integration, identification of social support) and parenting Skills
Non-adherence	Education and problem-solving strategies
Cognitive disturbances	Mindfulness-based training (to cultivate patients' self-awareness and focused attention) Interventions focusing on compensatory strategies and cognitive re-training Acceptance and commitment therapy (nonjudgmental acceptance of cognitive disturbances and refocusing on the achievement of valued life goals despite the impairment)
Psychoeducation	Sessions focusing on dissemination of knowledge and education regarding seizures, comorbid psychiatric conditions, available modes of treatment and lifestyle challenges

3. *Disability evaluation*

The Rights of Persons Disability (RPWD) Act 2016, under the section of 'chronic neurological conditions' exemplifies multiple sclerosis and Parkinson's disease. Non-traumatic epilepsy as such has not been specifically mentioned under this section. However, particularly in those cases which are intractable, it could also be considered as a chronic neurological condition. These cases can hence be certified under the same category as per the RPWD Act 2016. However, at present, there are no clear guidelines as to how to calculate the severity of disability for epilepsy. Owing to inherent psychosocial issues and stigma related to epilepsy, these individuals have problems in travelling, work and leading a normal life as a part of the society. Hence, clear guidelines regarding the certification of epilepsy are urgently needed. It should be noted that individuals presenting with seizure disorder along with a psychiatric disorder will have to be certified under the provision of multiple disabilities as per RPWD Act, and will have to be done in conjunction with a neurologist.

Special issues:

Table 12: Special issues in epilepsy

Special population	Strategies
Cognitive impairment	• Causes: 1) Duration and frequency of seizure 2) Effect of AEDs, control of seizures 3) Structural abnormalities on MRI. • Subjective cognitive complaints are quite common in epilepsy patients.(44 to %) However on examination such cognitive impairment is not present in these patients. This might be due to concurrent depression and anxiety disorders. • In elderly patients at the onset itself if cognitive functioning is affected, clinically significant impairment may develop gradually.

	• Generalised cognitive impairment is seen with idiopathic generalized epilepsy, whereas TLE is associated with memory impairment. However TLE causes wider network dysfunction leading to other cognitive deficits too. A major concern has been about progressive decline in cognitive functioning. There are mixed findings about this in literature. • Another question is whether cognitive impairment persists in spite of seizure control and it has been observed that minor deficits persist especially if there is underlying pre-existent brain damage. • Epilepsy surgery is also associated with cognitive impairment. An estimated 44% risk of verbal memory problems and 34% risk of naming difficulties was found in a systematic review. Resection of dominant temporal lobe, normal memory score before surgery, late onset, no hippocampal sclerosis and poor seizure control are some of the predictors of memory problems postsurgically.
Suicidality	• Patients with epilepsy are at an increased of committing suicide. 3 to 7% patients commit suicide. The risk of suicide is 4 to 5 times higher in patients with epilepsy than the nonepileptic population. Temporal lobe involvement in focal dyscognitive seizures increases this risk 25 times. • Suicidality also shows a bidirectional relationship with epilepsy, thus increasing the risk of epilepsy 5 times in patients with suicidal tendencies. • Causes of suicidal thought, suicide attempts and completed suicides in epilepsy are many. Psychosocial consequences of epilepsy, associated mood disorder in the form of severe depression, command hallucinations during ictal period, agitation, borderline personality traits are some of the reasons for suicidality. It is also suggested that suicidal risk increases due to some antiepileptic medication, though evidence does not yet support this finding. • An assessment for suicidal ideation and suicidal behaviour is very essential for prevention and early intervention.
Personality changes	• Particularly in those with TLE, certain behavioural traits have been classically described, including social viscosity (tendency to prolong social encounters), humorlessness, circumstantiality, hyposexuality and obsessionalism. These have been seen more commonly with left sided TLE or GE as compared to those with right sided foci. • Other studies have demonstrated hyper-religiosity to be associated with bilateral temporal lobe foci. This specific pattern of inter-ictal personality syndrome has been commonly labelled to as Gastaut Geschwind syndrome.

	• Personality traits such as emotional instability, immaturity and disinhibition have been noted in patients with JME, and have been thought to be a consequence of frontal lobe pathology. • A thorough evaluation including detailed history of symptomatology and assessment of personality (including psychological tests) is required. • The potential role of AEDs in the presentation of certain symptoms (such has irritability, hyposexuality) also needs to be kept in mind since these could be a result of side effects of AEDs.
Aggression	• Aggression could be a direct consequence of ictal phenomena or can be related to a complex interplay between the underlying personality, comorbid psychiatric disorders and psychosocial stressors. • Peri-ictal aggression is classically non-specific, purposeless, disorganized and generally directed towards things in the immediate vicinity. • Instances of aggression have particularly been noted in cases where patients are restrained since it is associated with the worsening of confusion. • A detailed evaluation of the type, intensity, frequency of the aggression episodes, its temporal connection with seizures along with video EEG may be required to understand the exact picture. • Management of aggression is generally directed towards treatment of the cause. In cases where aggression is suspected to be a result of seizure activity, prompt control of seizures with AEDs will help in preventing fresh episodes of violence. • In cases where aggression is related to a comorbid psychiatric disorder such as depression or psychosis, treatment of these conditions may help in reducing instances of aggression.
Children	• In the younger children, epilepsy is frequently associated with attention deficit hyperactivity disorder (ADHD) and autism. • In older children and adolescents, it is associated with behavioral problems, mood and anxiety disorders, personality disorders and psychotic disorders. • ADHD commonly presents as inattentive type and is seen 2-3 times more commonly in epilepsy as compared to general population. • As per current literature based on multiple RCTs, methyphenidate 0.3-1 mg/kg can be safely given for ADHD even in children with epilepsy with no added risk of seizure worsening. • Data on atomoxetine and amphetamines are lacking, hence should only be prescribed in case of non-response to methylphenidate based on an informed decision and with proper clinical monitoring.
Epilepsy surgery	• Following epilepsy surgery mood disturbances in the form of depressive features or lability occurs in the first 6 to 12 weeks. This is seen in almost 25% patients and especially in

	those with temporal lobe surgery. In 10% patients depressive features persist requiring treatment for the same. • Interictal psychosis may arise for the first time after surgery. • The large Multi-centre Study of Epilepsy Surgery trial has shown that there is improvement in depressive features following surgery if there is good seizure control post surgically. • Hence it is necessary to evaluate for mood disturbances after surgery, follow up regularly to see if they persist, also see the seizure control with surgery and accordingly decide to treat these patients. On the other hand, it is essential to rule out depression in presurgical evaluation, as history of depression is associated with poorer seizure control after surgery.
Substance use disorders:	Substance use can lead to seizures in intoxication, in over dose, in withdrawal and in long term toxicity. This can lead to non-adherence to treatment in seizure disorder and poor seizure control. In an Indian study conducted in 450 prisoners it was found that prevalence of epilepsy was 1.4 times higher among substance using prisoners than in non-substance using prisoners. Alcohol, cannabis and opioids were the most commonly used substances. (Refer to table)

Table 13: Substance use disorders and seizure

Substance use disorder	Pathophysiology	Treatment
Alcohol: Chronic use and withdrawal	Hypokalemia, head injury, clotting problems with cerebrovascular hemorrhage lead to lowering of seizure threshold, also chances of prolonged seizure activity. During withdrawal there is hyperexcitability of neurons, kindling, sleep deprivation all reducing seizure threshold.	Single seizure in withdrawal- Benzodiazepines for 7 days and vitamin supplements for treatment of withdrawal Multiple seizures, withdrawal related- Psychoeducation for prevention of further seizures Multiple seizures during withdrawal with uncertain etiology- Long term treatment with AEDs. Phenytoin, Carbamazepine,

		Phenobarbital not preferred(risk of hepatic induction), Valproate not preferred(may lead to further hepatic damage). Preferred AEDs- Levetiracetam, Lamotrigine, Topiramate.
Opioid	Opioid receptor changes, mu receptor agonism(seen in animal models) may induce seizures. Metabolic disturbances, intracranial pathology can also cause seizures.	Benzodiazepines
Cocaine	Serotonergic mechanisms. Seizures are not dose related.	Usually self limiting.
Amphetamines	NMDA toxicity, Hyponatremia	Management of hyponatremia, psychoeducation, management of amphetamine dependence.
Benzodiazepines	Unmasking of downregulation of GABAergic inhibition and upregulation of the glutamatergic system due to chronic use during withdrawal.	Long acting benzodiazepine like Diazepam or Chlordiazepoxide in gradually tapering doses.

Functional Neurological Symptom Disorder with attacks or seizures and Epilepsy:

Functional neurological symptom disorder with attacks or seizures (Popularly known as Psychogenic non-epileptic seizures or PNES) is characterized by episodes of seizure like activity. But without any seizure activity on video EEG. Like epileptic seizures, PNES present as paroxysmal time-limited, alterations in motor, sensory, autonomic, and/or cognitive signs and symptoms, but unlike epilepsy, PNES are not caused by ictal epileptiform activity. Sometimes it is difficult to differentiate between epilepsy and PNES. It is essential to diagnose PNES correctly, otherwise patients get exposed to antiepileptic medication unnecessarily and may suffer from toxicity of these medications. It leads to repeated hospitalisations too. There is a psychological basis for the symptoms in PNES. Unless a correct diagnosis is made these psychological issues are not handled and the patient keeps visiting the emergency services repeatedly.
PNES is seen in 10-40% of long term cases of epilepsy and around 10-15% cases of PNES have a seizure disorder. According to a study by La France et al the time gap between the onset of symptoms and diagnosis of PNES is between 1 to 16 years.
PNES is seen more commonly in women between 26-32 years, however it is seen in children and at times in elderly too. It is not seen in preschool age group and the incidence increases with age of the child.
National Association of Epilepsy Centres has given a guideline to refer a patient of suspected PNES and if seizure disorder is not controlled by AEDS for more than a year to Specialized Epilepsy clinic.
Diagnosis of PNES:

A detailed history, clinical features and investigations help in diagnosing functional neurological symptom disorder.

Table 14: Differences between Epilepsy and functional neurological symptom disorder.

Epilepsy	functional neurological symptom disorder.
Most common in young children and elderly	Most common in young age group between 20-40 years
Risk factors are infections, genetic metabolic disorders	Risk factors are stress, trauma, scholastic difficulties, interpersonal problems, physical abuse, sexual abuse
Clinical features	
Duration: <2 minutes	>2 minutes
Movements- Synchronous, symmetrical clonic activity in GTC seizure Tonic rigidity at onset of GTC seizure	Asynchronous movements, Asymmetrical, out-of-phase movements, pelvic Thrusts sometimes, and hyperarching at times
Sleep : Occurs in physiological sleep	Usually occur while awake
Head rotation movements: Absent	Present
Amnesia for activities during episode	Recall intact during the episode
Pupillary reaction altered or dilated pupils	Pupillary reaction unchanged
Heart rate: Increases rapidly during the seizure	Inconsistent increase in heart rate
Urinary incontinence usually present	Rarely present
Epileptic cry- monotonous, meaningless phrases or sounds	With a feeling tone usually sad, coherent speech
Eyes mostly open and when closed, not throughout the episode	Eyes closed throughout the episode.
Tongue bites more common and on lateral side	Tongue bite less common and on tip or on lip or cheeks
Fractures or ecchymoses more common, burns occur mostly with epilepsy.	Ecchymoses or fractures less common. Rug burns or excoriations along long bone surfaces more common
Gradual recovery postictally	Immediate recovery after the episode
Focal neurological deficits, stertorous breathing and physical complaints seen.	Focal neurological deficits, stertorous breathing and physical complaints not seen.
Postictal headache seen commonly.	Interictal headache present commonly
EEG-Abnormal epileptiform activity and	Motor activity interspersed with normal background activity
Video EEG- Abnormal discharge and slowing of background	Normal background activity before, during and after the episode
Serum prolactin levels- High(>60->900 IU/ml)	Normal prolactin levels

Management:

Patients with PNES present in emergency services majority number of times. The goal of treatment in the emergency setting is to make patient symptom free.

1. Use of suggestion for the same
2. Techniques like social isolation
3. Psychoeducation of caregivers and garnering support
4. Confirm the diagnosis of PNES when patient follows up in OPD : Diagnosis of PNES is made on the basis of history, nature of seizure like episode, investigations like videoEEG, which is the 'gold standard' , psychological tests when necessary.
5. Rule out seizure disorder, other neurological disorders.
6. Ask neurologist to taper AEDs.
7. Establishing rapport with patient
8. Establishing the connection between psychological stress/trauma and PNES
9. Cognitive behaviour therapy for improving coping skills, for detecting cognitive distortions and correcting them.
10. Strengthen psychosocial support
11. Assess for comorbid anxiety disorder or depression.
12. If diagnosed start medication for the same.

    It has to be kept in mind that in primary care setting EEG, video EEG or even psychological tests would not be available. Then a good clinical history is the key to the correct diagnosis.

Conclusion

This CPG looks at the common psychiatric issues seen in PWE and provides pharmacological and psychosocial approaches towards management of these issues. It is important to take a detailed history focusing on understanding the temporal association between psychiatric symptoms and seizure episodes. Clinicians also need to be aware of possible pharmacokinetic and pharmacodynamic interactions between AEDs and other psychotropic drugs as well as the risk of de-novo psychiatric symptoms with certain AEDs. Due to the chronic nature of epilepsy, the co-morbid psychiatric issues and the associated stigma due to both, psychosocial interventions have an indispensable role in the management plan. Timely diagnosis of psychiatric disorders in epilepsy and effective management of these disorders is advantageous for the patient in terms of improved drug adherence, better functioning and quality of life.

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MANAGEMENT OF PSYCHIATRIC DISORDERS IN CANCER

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Abstract

Psychiatric disorders are increasingly being diagnosed in those with cancer. The psychiatric co-morbidities commonly seen are depressive spectrum disorders, adjustment disorders, anxiety disorders, sleep and sexual disorders. Psycho-oncology is an emerging specialty which is an intersection between oncology and psychiatry. It is important to recognize and treat the co-morbid psychiatric illness which in-turn will result in the improvement of Quality of Life (QoL) of those living with cancer. The assessment, investigation and treatment – pharmacological and non-pharmacological when tailor made for their specific needs are seen to be more effective. This chapters covers details of management of psychiatric disorders in cancer patients.

Introduction to psychiatric disorders in psycho-oncology

Psychiatric disorders are seen at an increasing rate in those diagnosed with cancer. The most common psychiatric disorders that are seen are depression, adjustment disorders, anxiety, sexual dysfunctions, sleep disorders and delirium, which combined affect at least 30-40% of

patients diagnosed with cancer. An even higher percentage of patients in an advanced phase of illness are diagnosed with psychiatric disorders. However, the psychiatric disorders are underdiagnosed and under treated, affecting the quality of life of a person with cancer. Currently with advancement in research and availability of newer drugs, with less side-effects and better tolerance, has been a boon for clinical psycho-oncology. There has been growing evidence for use of non-pharmacological interventions to reduce distress and treat psychiatric disorders. Hence, psycho-oncology is becoming a specialized novel area, integrating psychiatry, psychology into the care of oncology.

The definition and various aspects of psycho-oncology have been covered in different chapters of a recent book on psycho oncology [1]. The detailed description of each is beyond the scope of this chapter. Here we focus on the most common psychiatric disorders, their assessment and treatment focusing on the pharmacological and non-pharmacological aspects. We have looked at literature and guidelines from various countries and made a comprehensive summary of all which can start as the beginning point for formal guidelines for the Indian setting. These guidelines will enable a standard care and uniformity in procedures and practices across hospitals in the country. This is in hope of also intriguing clinicians and researchers to focus on specific areas of psycho-oncology and develop the guidelines further.

General Principles of pharmacological management in psycho-oncology:

1. For all drugs – start low and go slow, i.e. to start at the lowest possible dose and up titrate gradually based on need and tolerability. To stop at the minimum effective dosage for an individual.
2. Look for drug interactions, and adverse effect profile of the drug before initiating pharmacotherapy. Due consideration should be given to pharmacokinetic and pharmacodynamic properties of the drug, as people with cancer can have deranged metabolic parameters.
3. Not much is known about interaction of chemotherapy, radiation therapy and newer modalities of cancer treatments on the pharmacological properties of psychotropics. However, the clinician should take a very careful judgement about the medication that might suit the profile of the patient best.

4. The utility of non-pharmacological interventions should be emphasized and should begin as a mainstay modality in mild and mild-moderate psychiatric disorders.
5. A routine information of use of any ayurvedic, homeopathic or other medication should be looked at as psychotropics can have interactions with these medications.

Table 1. Drug interactions of psychotropics and Anticancer medications

Anticancer drug	Psychotropic	Interaction	Mechanism of interaction	Recommendation
Carmustine, Dacarbazine Nilutamide, Tamoxifen Gemcitabine	Naltrexone	Hepatotoxicity	Unknown	Avoid concurrent use. Periodic monitoring of patient's liver function and watch for signs and symptoms of hepatotoxicity.
ACDs with * in foot notes.	Clozapine	Myelosuppression	Additive synergistic effect	Clozapine should be avoided when person is on treatment with ACDs
Cyclophosphamide Ifosfamide Doxorubicin Etoposide	Fluvoxamine	Increased dose of ACDs	CYP3A4 inhibition by fluvoxamine	Prescribe with caution, reduce dosage od AD/ switch to a

Dexamethasone Methylprednisolone Prednisolone Prednisone Vinblastine Vincristine Vinorelbine Toremifene Tamoxifen				safer AD
Cyclophosphamide Ifosfamide Sorafenib	Bupropion	Increased dose of AD	ACDs inhibit CYP2D6 which reduces clearance of bupropion	Look out for signs of bupropion toxicity like agitation, anxiety, tremor, insomnia, seizures or neuropsychiatric symptoms
Imatinib	**Anti-Alzheimer's agents **Antipsychotics **Hypnotics and anxiolytics	Increased doses of psychotropics	Inhibition of CYP2D6 and/or CYP3A4 by imatinib.	Dose adjustments when Imatinib is introduced or taken out from chemotherapy.

	**Selective serotonin-reuptake inhibitors **Tricyclic antidepressants **Other antidepressants **Other psychotropics			
Imatinib	Bromocriptine, fluoxetine, sertraline	Increased concentrations of both ACD and AD	Inhibition of cytochrome P450 by both ACD and AD	To look out for serious adverse effects such as oedema, hematologic toxicity and immunosuppression.
Methotrexate	Haloperidol	Increased risk of haloperidol induced photosensitivity	Unknown	Patients should be advised to avoid exposure to sunlight or bright lights, and monitored for photosensitivity

				reactions during concurrent therapy
Tamoxifen	Antidepressants (tricyclic AD, lesser probability for selective serotonin reuptake inhibitors) Antipsychotics (Phenothiazines, Butyrophenones)	Increased risk of drug-induced QTprolongation andtorsades de pointes.	Additive effects of blocking potassium channels.	Measurements of QT intervals and Watch for symptoms of torsades de pointes (e.g. dizziness, palpitations, or syncope). If marked QT prolongation occurs, dose reduction/stopping the offending agent should be considered
Tamoxifen	SSRIs-citalopram, fluoxetine, paroxetine, sertraline	Increased plasma level of tamoxifen	Inhibition of CYP2D6-mediated metabolism of tamoxifen to endoxifen.	Dose adjustments of SSRI when Tamoxifen is introduced or taken out from chemotherapy.

Foot notes: ACD- Anticancer drug, AD- Antidepressant.
ACDs with *: Cyclophosphamide, Dacarbazine, Mechlorethamine, Melphalan, Procarbazine, Temozolomide, Rituximab,Trastuzumab, Bleomycin, Doxorubicin,Epirubicin,Etoposide,Irinotecan,Topotecan, Carboplatin,Cisplatin,Oxaliplatin, DocetaxelPaclitaxel, Vinblastine, Vincristine, Vinorelbine, Cytarabine, Fluorouracil, Gemcitabine, Methotrexate, Pemetrexed
**Anti-Alzheimer's agents(donepezil, galantamine)
**Antipsychotics(Aripiprazole,chlorpromazine,fluphenazine,haloperidol, olanzapine,prochlorperazine,quetiapine, risperidone,trifluoperazine,ziprasidone)
**Hypnotics and anxiolytics(alprazolam,chlordiazepoxide,clonazepam, diazepam,flurazepam, midazolam,promethazine, propanolol,zolpidem)
**Selective serotonin-reuptakeinhibitors (citalopram,paroxetine)
**Tricyclic antidepressants(amitriptyline,clomipramine, doxepin,imipramine, nortriptyline)
**Other antidepressants(mirtazapine, venlafaxine)
**Other psychotropics(atomoxetine)

Box 1. Anticancer drugs that do not have any known interactions with psychotropics

Capecitabine
Lomustine
Anastrozole
Exemestane
Fulvestrant
Goserelin
Letrozole
Leuprolide
Mitoxantrone
Alitretinoin
Leucovorin
Mesna

Brief introduction:

At this stage we have understood the need for psycho-oncology, the various disorders associated with the diagnosis of cancer. Now we will look at the nuances in the assessments and treatment of individual psychiatric disorders with respect to psycho-oncology.

Depressive disorders

Introduction

In cancer patients, depression is one of the most commonly diagnosed psychiatric disorders[2]. The incidence of major depressive disorder can range from 15-40%. Depressive disorders can be on a spectrum and can include major depressive disorders, persistent depressive disorders, dysthymia, adjustment disorder and demoralization syndrome. The diagnostic guidelines like ICD 10 or DSM V can be used to make a diagnosis. However, clinician should be aware that there is a significant overlap in the biological symptoms of depression and symptoms of cancer or adverse effects of the treatment. It is important to be able to delineate the symptoms and make a correct diagnosis of depression. There are various approaches described below:

- Inclusive approach - to include all the symptoms irrespective of the fact that these symptoms may or may not be attributable to cancer
- Substitute approach - to replace somatic symptoms with cognitive-affective items (Endicott's criteria)[3]
- Alternative approach - to add some new affective symptoms to the original criteria ((Akechi's criteria)[4]
- Exclusive approach - to exclude somatic symptoms and use only affective symptoms to make the diagnosis (Cavanaugh's criteria)[5]

For more details on the various approaches, readers are encouraged to read the references mentioned. Depressive disorders when identified and treated improve the quality of life and decision-making capacity.

Assessment

A detailed assessment must be done with regards to a good history on independent symptoms, current treatment, past psychiatric history, family history and substance use history.
Scales that help understand the intensity and severity are:

- Brief Symptoms Inventory (BSI)
- Hospital Anxiety and Depression Scale (HADS) are widely used to assess psychological distress. These are specifically designed to detect depressive symptoms in medically ill patients.

Other scales:

- CES-D (Centre for Epidemiological Studies –Depression)
- BDI (Beck Depression Inventory) have acceptable sensitivity and specificity in cancer patients.

Box 2. Contributors for depression	**Box 3. Those at higher risk of developing depression**
• Vitamin B12 deficiency • Hypothyroidism • Folate deficiency • Anaemia – Iron deficiency • Electrolyte imbalance	• Inadequate pain control • Life stress or loss • Past history of depression • Level of physical impairment • Patients with lung, gastric, oropharyngeal and gastric cancer • Substance use • Brain tumor, vascular vulnerability, Parkinsonism, Lewy body disease • Family history of depression • Poor coping skills

Box 3. Medications that can cause depression
• Hormonal agents including aromatase inhibitors, gonadotropin releasing hormone analogs, and selective estrogen-receptor modulators • Chemotherapeutic agents- Prednisone, dexamethasone, vincristine, vinblastine, procarbazine, asparaginase, tamoxifen, interferon, and interleukin 2 • Opioids

- Amphotericin B
- Statins
- Varenicline

Management:

When beginning treatment with cancer patients with depression and their families, information and support are provided, a time for appropriate decision and informed consent, support for families and care givers, being respectful of, and sensitive to, diverse familial, cultural, ethnic and religious backgrounds, coordination of cancer care and choosing depression treatments. NICE guidelines have given flowchart for step wise care for depression in people with cancer. The same is given in figure 1. The management of mild, moderate, severe depression are discussed in the previous **IPS guidelines on depression** and should be referred to for treatment of depression in cancer as well.

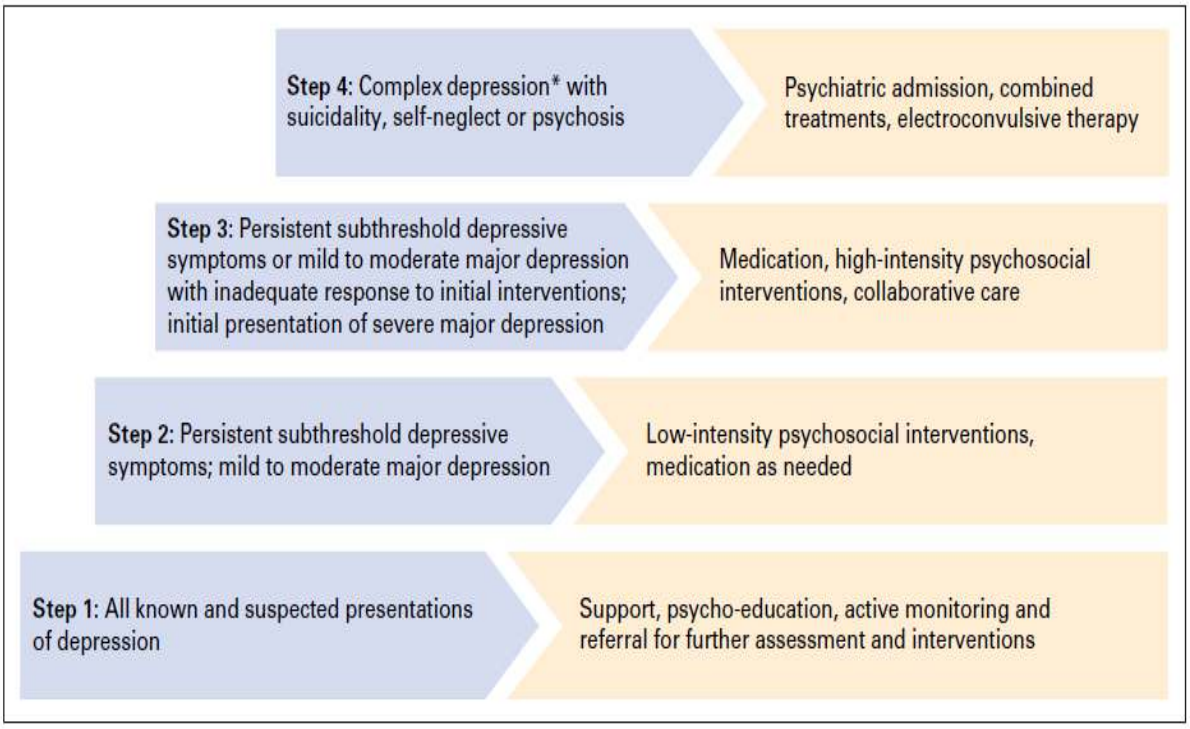

Figure 1. Stepped care model for delivery of care[6]**(adapted with permission).**

Pharmacological management

According to psychopharmacological studies, there is evidence that ADs are more effective than placebo in both cancer patients with major depression or depressive symptoms and in those with other cancer-related distressing symptoms[7]–[9]. However, considering poor health status and adverse effects the utility of ADs should be restricted to those with moderate to severe depressive episode. Those with mild depression should be started on ADs if psychosocial intervention does not produce desired change in mood or activity.

Guidelines for use of antidepressants in cancer patients:[1]

• Start the treatment at low doses followed by a period of dose titration to achieve an optimum individualized response (low doses may help to avoid unwanted initial side effects, particularly in patients in poor physical conditions).

• Inform and reassure patients of latency period and possible side effects, in order to avoid premature drop-out, especially if patients are receiving other medications.

• Treat the patient for 4-6 months in order to avoid relapses or new episodes of depression after remission.

• Regularly monitor the patient's physical variables and concomitant use of medications for cancer (e.g., steroids, antiemetics, antibiotics, antiestrogen and chemotherapy agents).

• Discontinue medications by tapering the dose by 50% over a couple of weeks to reduce the risk of withdrawal symptoms that can be distressing and may be mistaken for symptoms of cancer illness or relapse into depression.

• Reassurance and education of the patients are extremely important in oncology settings.

Most of the evidence comes from case studies or open trials, and as per current research and guidelines practiced SSRIs are the first line of treatment as they have a lesser side effect profile. Currently,

1. SSRIs- The most commonly used medications are citalopram, escitalopram and sertraline are used to treat depression in patients with cancer and also are found to be beneficial for anxiety and hot flashes. Duloxetine an antidepressant along with treating depression, also has benefits in chronic musculoskeletal pain, chemotherapy induced peripheral neuropathy and neuropathic pain.

2. SNRIs- Venlafaxine and desvenlafaxine are used to treat major depression, anxiety, neuropathic pain
3. TCAs- For neuropathic pain, have to be used judiciously as they can have severe and intolerable side effects like constipation, dry mouth and sedation.
4. NASSA- Mirtazapine can be used to treat sleep disturbances and nausea, the metabolic adverse effects have to be kept in mind.

Non-pharmacological management

The type of therapeutic intervention must be given due thought considering symptoms and factors that contribute to depression. Recently diagnosed patients with cancer with mild to moderate depression may benefit from psychoeducation, cognitive behavioral therapy (CBT), relaxation strategies, and problem-solving approaches[10]. Patients who have more advanced disease may benefit from supportive-expressive psychotherapy that focuses on processing fears associated with death and other existential concerns[10]. Recent development of Manualized targeted psychotherapies for those with advanced illness, include Meaning-Centered Group Therapy[11], Dignity Therapy[12], Mindfulness-Based Meditation Therapy[13] and a brief supportive-expressive intervention referred to as CALM[14](Managing Cancer and Living Meaningfully).

Table 2. Description of Psychological Interventions

Term	Description
Counseling	Generic term used to refer to supportive psychosocial care provided by a qualified professional
Psychoeducation	Provision of information designed to increase knowledge and reduce uncertainty and

	thereby enhance psychological well-being
Relaxation training	Teaches skills for releasing physical or mental tension using meditative activities, progressive muscle relaxation exercises, or use of guided mental imagery
Problem-solving therapy	Focuses on generating, applying, and evaluating solutions to identified problems
Cognitive behavioral therapy	Focuses on identifying, challenging, and changing maladaptive thoughts and behaviors to reduce negative emotions and promote psychological adjustment
Interpersonal therapy	Focuses on problems within interpersonal interactions and relationships, emphasizing areas such as grief, role transitions, disputes, or interpersonal deficits to reduce distress and promote psychological adjustment
Supportive-expressive (psychodynamic) therapy	Focuses on the communication and processing of subjective experience and on the joint creation of meaning within a therapeutic relationship to reduce distress and promote psychological adjustment (eg,

	Meaning-Centered Therapy, Dignity Therapy, and CALM)

Demoralization:

The term demoralization was first described by Frank Jerome in 1970s. Demoralization is considered as a normal reaction to a particular situation. Usually the situation is a medical illness, like cancer, treatment for their condition etc. It can co-exist with other psychiatric disorders like depression, anxiety, adjustment disorder and others. The Table no.. below enumerates the ways to distinguishdemoralisation from other psychiatric disorders.

Table 3. Differentiating points for various Psychiatric conditions seen in Cancer[15]

	Depression	Demoralization	Adjustment disorder	Anxiety disorders
Duration of symptoms (minimum)	2 weeks	2 weeks	Usually have a stressful event/change and symptoms start <1 month of change.	Symptoms which last for most days of a week for a few weeks.
Stressor	+/-	+	+	+/-
Affective symptoms	Sad/Depressed +/- anxiety	existential distress, including hopelessness or loss of meaning and purpose in life.	Excessive worry, anxiety, depressive symptoms,	Anxious affect
Cognitions	Helplessness, hopelessness, worthlessness.	pessimism, helplessness, sense of being trapped, personal failure, or	Sense of low confidence, difficulty in coping.	Fear of negative consequences, usually related to the future.

		lacking a worthwhile future, subjective sense of self incompetence, may extend to hopelessness.		
Arousal symptoms	Present only when associated with anxiety symptoms.	None	Can be present when exposed to stressor.	Usually, present.
Motivation, hedonic pleasure	Amotivation Anhedonia	Motivation present, but dilemma in direction of action. In severe cases can have amotivation. Hedonic pleasure preserved.	Motivation present, but dilemma in direction of action. Hedonic pleasure preserved.	Motivation preserved. Hedonic pleasure preserved.
Sleep	Insomnia, usually early morning awakening	Usually sleep intact	Can have insomnia.	Can have insomnia.
Pervasivity	Pervasive	Non-pervasive.	Get better with removal of stressor or change in environment	Can be pervasive to situation specific.

Anxiety disorders

Introduction

Among patients with cancer, anxiety is a common response to threats of uncertainty, suffering, and mortality. In cancer centers anxiety to a mild degree is seen in almost everyone with fluctuating levels and anxiety is highest at times of evaluation, surgery and other treatment/interventions. But anxiety at a disorder level[16] is seen in approximately 35% of cancer patents, this is higher than what is seen in general population. Clinical consequences are less effective medical decision making,3 worsening of medical symptoms,4 and disrupted cancer care[17]. Although anxiety and depression are highly comorbid, anxiety is independently associated with poorer quality of life among patients. Anxiety can be mild to severe in intensity. Among anxiety spectrum disorders we can find generalized anxiety, social anxiety, specific phobias, acute stress reaction, post-traumatic stress disorder and obsessive-compulsive disorder. The clinical symptoms and diagnosis usually made on the criteria as per ICD 10 or DSM V. The assessment scales used to assess are same as those that are used in depressive disorders.

It is important to note the possibility of a **Mixed anxiety depression**, where the symptoms do not amount to a complete anxiety/depressive disorder. This can be managed on the lines of mild depression/mild anxiety disorder.

Management

In mild anxiety disorders the first line of management is psychosocial management, in cases with poor response to treatment pharmacological management can be considered. In moderate to severe cases, pharmacological management combined with psychosocial treatment for adequate treatment.

Pharmacological management

The guidelines to start and treat with SSRIs in anxiety are like those in depression. SSRIs, benzodiazepines and non-benzodiazepine anxiolytics can be used to treat anxiety[17].

Benzodiazepine and non-benzodiazepine analogues can be used to treat anxiety acutely. They should be tapered and stopped at the earliest possible time. Clinicians should be aware about the potential of dependence, complications in those with alcohol abuse/dependence, paradoxical reactions in elderly and disturbance in concentration, drowsiness and possibility of falls in frail and elderly patients. The dosage should be given at minimum and titrated based on improvements, tolerability and adverse effect profile.

SSRIs that are used in cancer patients are citalopram, escitalopram, sertraline and SNRIs i.e. venlafaxine and desvenlafaxine can be used to treat anxiety as they have less interaction with other drugs. Clinicians should try and avoid fluoxetine, fluvoxamine and paroxetine as they can alter the levels of chemotherapeutic, hormonal therapy and can worsen nausea in cancer patients. Antidepressants can be used for longer duration as required.

Other anxiolytics are – buspirone, mirtazapine, atypical antipsychotics at low doses. Buspirone is a anxiolytic with no addictive potential, but has 2-3 weeks for onset of action. Mirtazapine is a good drug of choice when anxiety is associated with insomnia and anorexia as sedation and possible weight-gain which are side effects are seen to be beneficial here. A low dose atypical antipsychotic, such as olanzapine and quetiapine and anticonvulsants, such as gabapentin, are also used in the clinical practice for managing anxiety. These have not been approved by FDA and have not been adequately studied in patients with cancer.

Non-pharmacological management

Psychotherapy researchers have tested for an emerging base of mental health treatments for individuals with cancer, including educational interventions, cognitive-behavioral therapy (CBT), problem-solving therapy, mindfulness-based approaches, and supportive-expressive group therapy, among others[18].

Traditional CBT helps patients reframe irrational thoughts, beliefs that exacerbate anxiety and support in overcoming their fear and avoidance through gradual exposure to anxiety-provoking situations[19]. However, aspects of this approach may be less useful for patients with terminal cancer who must continually adjust to very real changes in disease status. Psychological

interventions can be tailored to address the specific concerns related to having incurable cancer, such as existential distress over poor prognosis; increased disability and decrements in functioning; perceived burden posed to family caregivers; and difficulty in managing fatigue, pain, and adverse effects resulting from anticancer therapies, advanced cancer receiving palliative care[20].

Acceptance and Commitment Therapy

ACT is a cognitive and behavioral intervention that uses acceptance and mindfulness processes, commitment, and behavior change processes, to produce psychological flexibility[21]. The six processes of ACT can be summarized as follows. Acceptance and diffusion both undermine destructive language processes; self as context and contact with the present moment both involve increasing effective contact with the here and now; values and committed action both involve building out the positive aspects of language into patterns of behavior change[22].

The application of ACT in community-based settings and group intervention has also been researched for anxious cancer survivors. Their findings demonstrate that relative to a month-long baseline period, ACT led to moderate to large improvements in cancer-specific and broader outcomes[23].

Mindfulness based cognitive therapy

MBCT includes mindfulness practices designed to cultivate nonjudgmental observation and acceptance of bodily sensations, cognitions, and emotions. Participants learn to engage in sustained observation of these phenomena, with an attitude of interest and curiosity, and to accept them as they are, without trying to change or escape them. MBCT also includes elements of cognitive therapy that are consistent with nonjudgmental acceptance of the experience. A decentral view of thoughts is emphasized, in which participants are encouraged to view their thoughts as transient mental events rather than as aspects of themselves or as necessarily accurate reflections of reality or truth[24].

Delirium

Introduction

Delirium is the most common neuropsychiatric disorder associated with cancer. It is associated with high rates of mortality, morbidity, increased burden on caregivers, increased length of hospital stay and health care cost[25], [26]. Delirium is usually undiagnosed, untreated or undertreated. Delirium is seen in 20-30% of people diagnosed with cancer and the incidence is 85% in those with terminal illness[27]. It can be caused due to various treatable and reversible causes, can also be due to irreversible causes as in terminal delirium. The causes are outlines in Box no 4[1]. The risk factors for developing delirium are given in Box 5[1]

Box 5. Reversible causes of delirium:

Cancer disease related

- Brain tumor and metastasis,
- Paraneoplastic syndrome,
- Ectopic hormone-producing tumor (ACTH, ADH, insulin-like,
- parathyroid hormone)

Cancer treatment

- Chemotherapy,
- Corticosteroids,
- Brain irradiation

Cancer pain drugs

- Opioid analgesics,

Antidepressants,

Psychostimulants

Other Drugs

- Benzodiazepines,
- Anti-cholinergic drugs,
- Alcohol

Infection

Metabolic disturbance

- Hypoxia,

- hypercapnia,
- Hypo- or hyper-glycemia,
- Vitamins (B12, folate),
- Electrolyte imbalance (Na, K, Ca),
- Anemia,
- dehydration,
- poor nutritional status,
- liver or renal dysfunction

Environmental

- Admission to hospital,
- Physical restraints,
- Bladder catheter

Box 6. Risk factors of delirium

- Age of 65 years or older
- History of delirium, dementia, cognitive impairment
- Low performance status, immobility, low level of activity
- Visual or hearing impairment
- Dehydration, malnutrition
- Many psychoactive and non-psychoactive drugs
- Alcohol abuse
- Advanced illness and coexisting medical conditions

Clinical signs

Delirium is characterized by an abrupt onset of disturbances of consciousness (ie, arousal), attention, cognition, and perception that fluctuate over the course of the day[25], [27]. The following are clinical signs seen in delirium:

- Disturbance in level of consciousness (alertness or arousal)
- Attentional disturbances
- Rapidly fluctuating clinical course and abrupt onset of symptoms
- Disorientation
- Cognitive disturbances (i.e. memory impairment, executive dysfunction, apraxia, agnosia, visuospatial dysfunction, and language disturbances)
- Increased or decreased psychomotor activity
- Disturbance of sleep-wake cycle, worsening of symptoms with sundowning.
- Mood symptoms (depression, dysphoria, mood lability, euphoria)
- Perceptual disturbances (hallucinations or illusions) or delusions
- Disorganized thought process
- Incoherent speech
- Neurologic findings (may include asterixis, myoclonus, tremor, frontal release signs, changes in muscle tone)

Subtypes of delirium:

There are three types of delirium based on clinical signs, Hypoactive subtype, hyperactive subtype and mixed type of delirium. **Hypoactive delirium** characterized by people who become withdrawn, quiet and sleepy and who do not express discomfort and distress. **Hyperactive delirium** showing restlessness, agitation and aggressiveness can be easily recognized. **Mixed delirium** is characterized with alterative periods of hyper and hypo active delirium. Patients with hypoactive delirium were as distressed as those with hyperactive delirium, and mortality rates are higher in hypoactive delirium as compared to hyperactive delirium.

Box 7. Subtypes of delirium:

1. **Hyperactive delirium**

2. **Hypoactive delirium**
3. **Mixed delirium**

Assessment

The assessment should involve focused history of symptoms of delirium, medications and treatment history, assess systemic comorbidities, signs of infection and all reversible causes of delirium. use tools to assess delirium. There are various tools to assess delirium, including the

- Memorial Delirium Assessment Scale (MDAS)[28]
- Delirium Rating Scale-Revised 98 (DRS-R-98)[29]
- Confusion Assessment Method (CAM)[30].

These scales are validated in patients with cancer and are used to maximize diagnostic precision for clinical and research purposes and to assess delirium severity.

After assessment and understanding the severity of delirium, we should assess for causes of delirium as mentioned in Box 4.

Management

After screening and assessment of delirium, any treatable causes must be addressed and periodically the delirium should be re-assessed to observe any improvements in the delirious state. The aim of treating delirium is to see a person conscious, alert, calm, comfortable, cognitively intact, not psychotic, not in pain and coherently communicating[27].

Pharmacological management

The various groups of medications have been tried to treat delirium in cancer patients. A summary of the available evidence is given below.

Look for the current ongoing medications, stop any drug with potential to precipitate or worsen delirium. The management of delirium is mentioned briefly here, we recommend the readers refer to **IPS guidelines on management of delirium** and adopt the same for management of delirium in cancer patients.

The following drugs can cause delirium:

- Anticholinergics (Benadryl, tricyclic antidepressants)
- Narcotics (meperidine)
- Sedative hypnotics (benzodiazepines)
- Histamine-2 (H2) blockers (cimetidine)
- Corticosteroids
- Centrally acting antihypertensives (methyldopa, reserpine)
- Anti-Parkinson drugs (levodopa)

The following medications can be used to treat delirium:

Antipsychotics(AP)- Haloperidol is the gold standard drug currently used to manage delirium. Haloperidol at doses of 0.5-1mg doses can be give IV or IM route hourly with baseline and regular ECG monitoring for risk of QTc prolongation. Haloperidol should be used with great caution in those sensitive to EPS and those with pre-existing dementia. Low dose chlorpromazine is an acceptable alternative. Second generation antipsychotics – Olanzapine, Risperidone and Quetiapine can be tried in hyperactive delirium and Aripiprazole in hypoactive delirium. The evidence for use of second-generation APs is limited.

Benzodiazepines- Benzodiazepines can be used in patients with agitation and distress. Midazolam and Lorazepam can be used as subcutaneous/intravenous/intramuscular routes. It should be used with caution in elderly – may cause falls, increased sedation, respiratory depression. They can also cause paradoxical worsening of agitation. Should start at the lowest

dose, around 0.5mg per hour, or 1mg can be repeated every two hours until the patient is sedated.

Psychostimulants- There have been case reports on use of methylphenidate with antipsychotics, one open label study using modafinil and antipsychotic combination to evaluate the efficacy of these drugs in cases with hypoactive delirium. Modafinil and methylphenidate have shown some positive efficacy in terminally ill patients. However, due consideration should be given to the possibility of drug induced exacerbation of psychotic symptoms or precipitation of agitation.

Cholinesterase inhibitors- Rivastigmine and donepezil, have been theoretically implicated to correct the cholinergic imbalance seen in delirium. However, they have not shown evidence to be beneficial in delirium. There have not been any studies done specifically in cancer. Hence use of these is not recommended in cancer patients with delirium.

There have been various studies looking at preventing delirium in acute care setting specifically in elderly. Various pharmacological agents like antipsychotics, melatonin, dexmedetomidine, rivastigmine and donepezil have been tried but the evidence is sparse and requires more robust clinical trials.

Terminal delirium [31]**:**

The role of sedation in terminal delirium is debatable. However, in some cases, palliative sedation may be required. Physicians should make this decision in discussion with the family and there should be documented informed consent.

- 1st line: Midazolam and Haloperidol as a combination –Titrate midazolam gradually to maximum dose of 20 mg / 24 hours – rarely up to 25- 30 mg/24h depending on control of agitation. Low doses of haloperidol, can be injected.
- If midazolam is ineffective IV infusion of Phenobarbitone / Pentobarbitone /Propofol. Dose is titrated until symptom control is achieved.

Non-pharmacological management –

Nonpharmacologic and supportive therapies play an essential role in the treatment and prevention of delirium in patients with cancer. Assessment and modification of key clinical factors that may precipitate delirium for persons at risk for delirium are, including cognitive impairment or disorientation, dehydration, constipation, hypoxia, infection, immobility or limited mobility, several medications, pain, poor nutrition, sensory impairment, and sleep disturbance, constitute the main components of nonpharmacologic intervention trials. Although these interventions were not found to have any beneficial effects on mortality or health-related quality of life when compared with usual care, there is evidence that they result in faster improvement of delirium and slower deterioration in cognition especially among older patients with delirium in general hospital settings[32].

Nonpharmacologic prevention strategies such as multicomponent intervention with multidisciplinary, educational, and proactive management of patients at risk for delirium are supported by the evidence-based literature in general hospital settings, especially among older patients. Although they may not be effective in controlling delirium symptoms, the use of nonpharmacologic interventions in patients with cancer who have delirium is recommended when feasible. There are no known risks associated with the use of nonpharmacologic interventions in patients who have delirium.

In a paper by Dr Richeimer, explains the has two levels of intervention - cognitive interventions and emotional interventions[33] that can be done by caregivers. The cognitive interventions help restore impaired cognitive functioning and the emotional intervention helps to deal with potentially overwhelming emotions, especially - fear and panic. The tables below illustrate the application of the two psychological interventions in Delirium and their components.

Cognitive interventions

Table 4: Cognitive interventions in delirium

Intervention	Method	Explanation	Example

Clarify	Correct misperceptions	It targets the tendency of the patient to misperceive his/ her environment. Orientation to place, date,day, time is useful.	“This room is not a laboratory but an ICU. All people here are trying to help you
Verify	Confirm accurate perceptions	Verification and validations help to compensate for the decreased ability to differentiate between real and not real	“Yes,there is a lot of strange equipment around you, but of all which is necessary to treat you”
Explain	Provide information about illness, treatment and current environment	Explanation compensates for patients' decreased ability to understand recent events, circumstances and environment.	‘The reason you are seeing things is because your kidneys are not working well. It is common to have hallucination with such problems”
Repeat	Useful information frequently repeated	Patients with delirium have impared memory. Frequent repetition	“Good evening. You may remember me from this morning. I’m Dr. A and it is

		of all interventions is important.	7pm, Monday, July 20th.

Emotional interventions

Table 5: Emotional interventions in delirium

Intervention	Method	explanation	Examples
Acknowledge feelings	Confirm the existence and reasonableness of patient's feelings	Delirious patients often are in a life-threatening situation and receiving intensive medical treatment. They are likely to fear not only death but also pain, abandonment, permanent capacity, and insanity.	I understand that you are feeling frightened. This is a pretty upsetting place. Other patients feel scared at times too.
Provide familiarity	Well known people and objects to be provided in their environment	Paucity of familiar sights and sounds intensifies the strangeness and fearfulness of the environment.	Same room, same medical team, Favorite tv shows.

Alleviate isolation	Allow for sharing of emotional burden	Sharing of emotional burden relieves distress and isolation.	“I can imagine that you’re afraid you might die here”
Fostering a sense of control	Allow patients control of the environment, body, treatment whenever possible.	For some, complete dependency on caregivers may be anxiety provoking. Regaining as much control as possible is important.	‘Here is the remote to adjust your bed, pls use it”
Balance of hope and realism	Provide realistic information with hope and optimism	For patients who are aware of the seriousness of illness, it is helpful to acknowledge it. To verify their perception of the situation. Denial of this, can make them lost trust in their medial team	“Yes you illness is serious, and operation does come with it risks, but doctors are very component and hopeful”

Delirium that develops in advanced cancer can contribute to high levels of distress for family members of the patient. One crucial component that must be emphasized within the multicomponent intervention is the education of family members/ secondary caregivers and improved their knowledge, emotional state and response towards the delirious patient.

However, rigorous evaluation of educational programs for family caregivers about delirium is needed. Caregivers who are educated about delirium are seen to be more confident and able to make good decisions.

Cancer related fatigue (CRF)

Introduction

NCCN guidelines define cancer related fatigue (CRF) as a "persistent, distressing, subjective feeling of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment" and when severe does not improve with rest (Fatigue 2018). CRF is also disproportionate to the activity levels and interferes with routine activities. CRF is seen in 40-100% of people with cancer [34]. CRF can be associated at any stage of illness(at diagnosis, during treatment or end of life care) and can even persist for few months to years' post-treatment. CRF impacts the Quality of life and its effect is both profound and pervasive. This disorder diminishes a person's ability to work, to participate in social, leisure, and other activities, and to sustain meaningful relationships with his/her family and others[34]**.** The mechanism of CRF remains elusive until date, however the implication of cytokines, interleukin, tryptophan degradation and other physiological and biochemical mechanisms have a role to play[35].

Assessment

The most important thing to understand in CRF is that it is a subjective experience, usually underdiagnosed and undertreated[36]. Hence, we stress the need for screening and evaluation of CRF, and re-evaluation at regular intervals to understand its burden on QoL and cancer care. MD Anderson symptom Inventory(MDASI) can be used to score the severity of CRF[37]. Similarly other scales that can be used are 10-point numeric rating scale(NRS) for fatigue[38] and brief fatigue inventory(BFI)[39].

The first and foremost step is to take a detailed history and focus on the symptom of fatigue and its associated symptoms. **A comprehensive and focused diagnostic assessment, with the aim to identify treatable contributing and comorbid conditions**[35]. In the history evaluate fatigue in the domains of the onset, course, duration of symptoms, factors that alleviate and exacerbate fatigue. In the history of associated symptoms look for emotional distress, weight changes, oral intake of solids and liquids – nutritional intake, sleep disturbance, activity levels, medications and treatment currently on, co-morbid conditions and substance use history. A detailed physical examination focusing on signs of anemia, dehydration, edema, jaundice and any other physical abnormalities. A detailed panel of investigations of complete blood count, Serum electrolytes, blood and urine culture – to look for any active infection, evaluate thyroid and gonadal hormones status when necessary. A list of treatable causes and contributing causes of CRF is given in table 4.

Table 6. Enlisting the treatable causes and contributing factors for Cancer Related Fatigue[40]

Treatable contributing causes	**Comorbid factors**
- Anaemia - Sleep related problems and poor sleep hygiene - Poor nutritional status/ Poor oral intake - Fluid and electrolyte imbalances - Emotional distress (Anxiety/Depression/other) - Low activity levels - Adverse effects of medication/ other modalities of treatment - Substance use	- Infections - Hypothyroidism - Hypogonadism - Cardiac/ Renal/ Hepatic/ Pulmonary/Neurological dysfunction

Management:

After screening and assessment of CRF, any treatable causes have to be addressed and periodically the CRF should be re-evaluated to note for any improvements. There has been improvement noted in cases where anemia, electrolyte imbalance or other treatable causes have been addressed. In cases where there are no identifiable treatable causes, one should evaluate the severity of CRF, stage of disease and for mild and mild-moderate cases non-pharmacological management is recommended, for moderate to severe and severe cases of CRF a combination of pharmacological and non-pharmacological management is recommended.

Pharmacological management

We should be aware that there are not enough clinical trials or consensus on the applicability of pharmacological management of CRF. Clinicians and researchers have tried to look at the utility of psychostimulants, antidepressants, corticosteroids and nutraceutical agents in the treatment of CRF. Here we describe a summary of the existing guidelines.

Psychostimulants - The class of psychostimulants includes amphetamines like methylphenidate, dexamphetamine and modafinil. Methylphenidate has shown to have some efficacy over placebo in clinical trials. Methylphenidate can be used in cases where there is no other identifiable cause for fatigue. It can be used in treatment, post-treatment and end of life care[40][41]. Dexamphetamine in clinical trials so far has not shown any positive results. Modafinil a non-amphetamine psychostimulant has shown positive results in those with severe fatigue, but not in those with mild to moderate levels of fatigue [42]. Modafinil has also shown benefits in patients with advanced disease in small trials but has not been replicated in larger trials.

Antidepressants - No antidepressant has been approved or shown to have high efficacy in targeting cancer related fatigue.

Corticosteroids - Methylprednisolone and its derivative dexamethasone are noted to improve CRF in people with terminal or advanced illness and receiving end of life care. One study also reported improvement in fatigue, general condition and absence/control of fluid retention[43]. A progestational agent, megestrol acetate has shown efficacy in cancer cachexia but not in

cancer fatigue[44]. Physicians must give due consideration to the adverse effects and toxicity of long-term use of steroids and should restrict its use in terminally ill patients with cachexia, also in those with brain and bone metastasis with pain.

Benzodiazepines- Eszopiclone is a sedative hypnotic, which has been tried and has not shown improvement in fatigue scores[45].

Nutraceuticals - L-carnitine deficiency showed that 1 g b.i.d. of L-carnitine supplementation ameliorated fatigue symptoms[46]. Coenzyme Q10, Wisconsin Gensing, astragalus, guarana and mistletoe are also been under experimentation and need more evidence towards its efficacy and benefits in treating CRF.

Research is currently focused on utility of modafinil, buspirone, American ginseng, L-carnitine, and coenzyme Q10 in CRF[34].

Non-pharmacological management

Forewarning patients about the symptoms of fatigue and providing information on strategies to alleviate it can provide some relief and reduce the anxiety of unexpected symptoms. If the patients are asked to discuss their fatigue, that in turn helps them to make the symptom more tangible and may reduce the uncertainty of its occurrence and associated distress[47]. A review looked at non-pharmacological treatment for cancer related fatigue showed benefits with: cognitive-behavioral therapy, exercises, hypnosis, relaxation and psychoeducation for fatigue[48]. There is also substantial evidence that physical activities, yoga and physically based therapies contribute positively to reducing cancer related fatigue[34].Interventions designed to increase the level of physical activity also had positive effects on QOL. Physically based therapies are those performed on a patient by a therapist or a lay person, such as massage therapies and acupuncture also were effective in reducing CRF Interventions such as group therapy, individual counseling, stress reduction with relaxation training, formal cognitive-behavioral therapy, education for fatigue management and support therapies have shown positive results.

Sleep disorders

Introduction

Insomnia in individuals with cancer ranges from 25 to 59 %[49]. These are usually associated with pain, hospitalization, medication, recurring thoughts about the disease and cancer-related fears. Anxiety and depression have been found to be highly correlated with insomnia[50]. Insomnia often persists for years and, when combined with already high levels of cancer-related distress, may place cancer survivors at a higher risk of future physical and mental health problems and poorer quality of life. While most of the studies in this area are correlative in nature, it is generally the case that sleep disturbance is: (a) positively correlated with fatigue, (b) more severe in fatigued than in non-fatigued patients and (c) a significant predictor of fatigue[51].

Assessment

All patients with cancer have to be evaluated for disturbance in sleep and assess if it amounts to a disorder level.

Screening: The National Institutes of Health (NIH) in a review of patient reported outcome measures [52] recommended two questions be used to screen for sleep problems:

(i) Do you have problems with your sleep or sleep disturbance on average for three or more nights a week? If yes

(ii) Does the problem with your sleep negatively affect your daytime functioning?

If answer to both questions is Yes, go for focused assessment.

A detailed history on the duration of sleep, total sleep time, sleep latency, wake time after sleep onset, napping during the day, excessive daytime sleepiness, quality of perceived sleep, circadian rhythm and sleep efficiency. Also assess beliefs about sleep, quality of life, co-morbidities, sleep log recorded over 2 weeks. This will complete the detailed evaluation of sleep.

Table 7. Predisposing, precipitating and perpetuating factors for insomnia.[53]

Predisposing	Precipitating	Perpetuating
- female gender - older age hyper-arousability as a trait - personal or family history - mood or anxiety disorders	- Cancer treatments that alter levels of inflammatory cytokines or disrupt circadian rhythms or sleep–wake cycles, - side-effects of cancer treatment, - menopausal symptoms, - hospitalization, - distress in response to cancer, - co-occurring symptoms, i.e. pain or fatigue, - medications such as corticosteroids	- excessive daytime sleeping, - long-term use of medications or use of inappropriate medications, - maladaptive cognitions,

Scales-

- Insomnia Severity Index (ISI)
- Edmonton Symptom Assessment System. *Revised(*ESAS revised)
- Pittsburgh sleep quality index for insomnia (PSQI)
- Epsworth sleepiness scale for increased sleep can be used

Pharmacological management

There are no specific guidelines or evidence-based approaches for treatment of sleep disorders in cancer. Non-Pharmacological management is the first-line management for insomnia.

Pharmacological management is used as a supplementary treatment modality to help the patient until they complete behavioral interventions or in those refractory to behavioral therapy[53]. The pharmacological management should be for short duration and should not exceed beyond 8 weeks[54]. Benzodiazepines should be used with caution as they have a risk of dependence. The approach should be lowest effective dose for shortest possible time[53]. Other drugs like Quetiapine, Trazodone, Melatonin have been beneficial. However, evidence in cancer patients and information on adverse effect or drug interactions is limited.

Non-pharmacological management

The recommended first-line treatment for insomnia is cognitive behavioral therapy for insomnia (CBT-I), a non-pharmacological treatment that incorporates cognitive and behavior-change techniques and targets dysfunctional attitudes, beliefs, and habits involving sleep[55]. Components of cognitive behavioral therapy (CBT) include:

- cognitive restructuring, such as restructuring negative thoughts, beliefs and attitudes related to sleep, and preventing excessive monitoring or worrying about getting enough sleep[56]
- behavioural strategies including stimulus control and sleep restriction in order to limit the time spent in bed during which the patient does not sleep.
- relaxation techniques that can be combined with both cognitive and behavioural interventions are quite useful when accompanied by visual imagery.
- basic sleep hygiene education includes suggesting the following to the patient: sleeping and waking up at regular times, relaxing at least 90 min before going to bed; creating a dark, comfortable sleep environment with a cool temperature, avoiding watching television, using a laptop, or working in bed, getting ample daylight during non-sleep hours, avoiding day naps, avoiding stimulants such as caffeine, nicotine and cigarettes 2–3 h before bedtime, avoiding intake of liquids 2 h prior to sleeping, and getting regular exercise but no closer than 3 h before bedtime.

Multiple psychological interventions – ranging from individual supportive psychotherapy to cognitive behavioral techniques (biofeedback, hypnosis, progressive muscle relaxation) – have proven to be effective in the control of anxiety and sleep disorders[57].

Sexual disorders

Introduction

Sexual health is an integral component of quality of life. It is a key component of physical, emotional well-being and quality of life, and is frequently negatively affected by cancer and its treatments. Unfortunately, sexual function concerns occur in 30–100% of cancer survivors [58], [59]. The sexual health is also impacted by psychosocial, mental health, previous trauma(if any), and cultural factors[60]. Cancer survivors experience a wide range of conditions like arousal difficulties, vaginal dryness/atrophy, decrease in orgasm intensity or frequency, diminished desire and sexual pleasure and dyspareunia. The sexual disorder further contribute to impaired body image and sexual-self-esteem[61]. Each of these aspects of sexual health may be affected by cancer and/or treatment, including systemic chemotherapy, immunotherapy, surgery, radiotherapy, hormonal therapy and other treatment modalities[58], [61]**.**Cancer patients want their treating physicians to provide information and help with the sexual consequences of cancer treatment, but hesitate to bring this up with their HCP [62]. Health care professionals believe that patients who want help with sexuality will bring up the topic themselves[63]. Amidst the chicken and egg situation, the necessary interventions to improve sexual health and QOL is hampered.

Assessment:

A detailed history of the aspects relating to desire, arousal, orgasm and resolution phase should be taken in detail. The onset, intensity, perceptions, cognitive distortions and level of impairment caused by the symptoms to the patient and the partner should be evaluated independently. Also, the level of communication, intimacy and perception of self and partner in relation to sexual problems should be assessed. A complete bio-psycho-social assessment will help in planning interventions for the person or couple in distress.

Management:

Interventions to improve sexual function and satisfaction in cancer patients and survivors suggests that a multidisciplinary approach, combining medical and psychosocial care, is the most effective strategy [64]. Providing information and counselling early in the process of treatment planning may be more effective than trying to restore sexual function after problems have become well-established.

The following are the interventions suggested by Cancer care Ontario(CCO) and American society of Clinical Oncology(ASCO), summarized here as per disorder[65].

1. Assessment – The health professional must bring up the discussion about sexual functioning and issues if any.
2. Body image- Psychosocial Counselling- individual or with the partner (if patient consents for partner to be involved).
3. Hypoactive sexual desire – In women, Fibanserin can be used in postmenopausal women. However, the evidence in this area is bleak. It should be as per judgement of the clinician.
4. Vasomotor symptoms in postmenopausal women- If the patient does not have a hormone sensitive cancer, hormone replacement therapy can be given. If patient unwilling for HRT can be started on Fluoxetine, paroxetine, venlafaxine, gabapentin or clonidine. Paroxetine and fluoxetine should not be given in women with hormone sensitive tumors. Adverse effects should be considered before initiating medications.
5. Vaginal dryness of pain – To start with lubricants or vaginal moisturizer, if no effective improvement low dose estrogen gels can be tried. For persistent introital pain, lidocaine gel can be tried. If no improvement further, selective estrogen receptor modulator ospemifene to postmenopausal women without breast cancer, in those with current or past history of breast cancer vaginal dehydroepiandrosterone can be given. These can be supplemented with vaginal dilators and pelvic floor exercises.
6. Erectile Dysfunction in men – First line of pharmacological management is Phospho-diesterase-5 (PDE-5) inhibitors, for cases not responding adequately to PDE-5 inhibitors a trial of vacuum erection device(VED) or intra-cavernosal injections can be given. If

there is no improvement with the above methods, one can consider surgical penile prosthesis implantation.

7. For loss of penile length – VED daily.
8. Vasomotor symptoms in men –Medications that can be used are venlafaxine, medroxyprogesterone acetate, cyproterone acetate, and gabapentin.

Non-pharmacological management

Sexual dysfunctions typically result from physiological damage related to cancer treatment, resuming a satisfying sex life requires good communication between partners[66]. They should also be encouraged to view that sexual pleasure and intimacy may include a variety of activities besides penetrative intercourse[59]. The first line of non-pharmacological interventions like cognitive behavioral stress management, relaxation training, sexual education, or sexual counselling may suffice to reduce sexual dysfunction in cancer patients or survivors[67]. In couples, partner participation during therapy may help enhance sexual intimacy and body image.Individuals are encouraged to reimagine sexual activity as a continuum of non-intercourse to intercourse activities as they become accustomed to their sexual changes.

Communication also plays an important role in navigating through various experiences of sexual dysfunction among cancer patients and issues around sexuality. A study evaluated sexual functions of patients diagnosed prostate cancer and their spouses and identified need for psychosocial interventions to facilitate healthy spousal communication and address the sexual rehabilitation needs of patients and their partners[68].

More intense interventions like Sensate focus therapy based on Master's and Johnson's model of sex therapy, Seeman's technique and Stop-start techniques for premature ejaculation are required in those where permission, information and specific suggestion to improve sexual functioning has not been effective.

Psychotic disorders

Introduction

Psychosis, more commonly Schizophrenia is seen in 1% of the population worldwide. However, nearly 50% of patients diagnosed with schizophrenia had significant delays between the diagnosis of cancer and initiation of treatment[69]. The various reasons for delay are the inability of people with psychosis to explain their distress, the bizarre descriptions maybe interpreted as a psychotic or a positive symptom and a detailed evaluation is delayed. Studies have noted that people with schizophrenia are most commonly diagnosed in advanced stages of cancer[70]. Some symptoms of schizophrenia can emerge secondary to brain tumors, chemotherapy and can be confused with symptoms of delirium. The preexisting or recent onset psychosis can have a negative impact on the quality of care, continuity of care, reaching remission as it is noted that a significant number of people are lost to follow up in 1 year. The quality of care is further poor in the homeless and institutionalized psychiatric patients.
The difficulty in following through instructions makes them more prone to side effects of surgery[71], chemotherapy and other treatment modalities. The mortality rates are higher because of adverse events in people with psychosis[72].
The management of psychosis in people with cancer is just as in general population, the psychiatrist should pay adequate attention to the ongoing cancer therapy and titrate the medications to reduce adverse effects.

Non-pharmacological management

Psychologists can support patients and informal caregivers to employ more effective coping strategies to deal with changes in personality and behavior. As hallucinations and psychotic symptoms can be very unsettling for both patients and their significant others. CBT for psychosis [73] or a combination with coping enhancement such as hallucination-focused integrative therapy, Mindfulness-based interventions[74] and acceptance and commitment therapy [75] for treating the emotional problems that may follow a psychotic episode have also been investigated, and show promising results.Psychiatrists with co-ordination in a multidisciplinary team can help the patient in understanding the clinical condition, need for treatment and assess the capacity to consent and make decisions[70] which can improve the outcomes and quality of life.

BREAKING BAD NEWS:

A bad news is “any news that drastically and negatively alters the patient’s view of her or his future”.

There are various methods employed to break bad news to people diagnosed, living with or in end stages of cancer journey.

The common steps in a clinical situation can be as follows. These can be varied and are flexible depending on the situation.

- Get all necessary information and prepare the place for the interaction. There should be privacy, and if the person wants a relative to be present.
- Check if the person wants to know
- Check what he/she already knows
- If the information is correct or partial, you can confirm or complete it. If the person does not know –
- Give a warning shot or a hint that something serious needs to be discussed
- Give a pause after the warning shot, to allow for any shock
- Tell about the diagnosis in simple words and terms, and wait for a moment for the person to understand it
- Provide realistic hope and plan for further care.
- Check what the person has understood and how he/she is feeling; also check if he/she wants to continue further interaction.
- Check immediate concerns and worries
- Provide necessary support
- Check feelings and encourage if the person has any questions. There may be many questions, some difficult, which can be handled as discussed above
- End with summarizing and extending full support of the team.

These can also be summarized as in box 8.

Guidelines for breaking bad news[1]
1. Breaking bad news starts with asking questions and assessing the patient's and family's readiness to grasp the information that is being conveyed. 2. An appropriate setting and privacy needs to be ensured. 3. Next, one should find out how much the patient already knows and whether they want any or more information. 4. After making sure that the patient is ready, the session should progress in a way that patient and family have a sense of control over the quantity of new information that is being received. 5. A 'warning shot' or an indication needs to be given at this stage, that something serious has happened, after which information is provided in steps. 6. After informing the diagnosis, it is important to pause, and acknowledge that the news could have shocked or distressed the person. 7. Further concerns or queries are explored and discussed and ventilation is facilitated. 8. Session is summarised and availability for a further session is emphasised.

The table 8 summarizes 2 other approaches for breaking bad news, the abbreviation and brief description are given. The readers are encouraged to go to the reference material for in depth understanding about it.

Table 8: Various protocols for Breaking bad news

SPIKES - The Six-Step Protocol for Delivering Bad News[76]	**BREAKS PROTOCOL FOR BREAKING BAD NEWS**[77]
- **S**ETTING UP the Interview	

- Assessing the Patient's **P**ERCEPTION - Obtaining the Patient's **I**NVITATION - Giving **K**NOWLEDGE and Information to the Patient - Addressing the Patient's **E**MOTIONS with **E**mpathic responses - **S**trategy and **S**ummary	- **B**ackground - **R**apport - **E**xplore - **A**nnounce - **K**indle - **S**ummarize

Role of spirituality in caring for the terminally ill[1]:

Palliative care the aims to keep the person comfortable, pain free and in good psychological and spiritual health and improve their quality of life until death. Spiritual care is an essential component of palliative care. All aspects of this definition including cancer pain, morale, family, and death and bereavement have a significant element of spirituality. Spirituality includes two main components: faith/religious beliefs and meaning/spiritual well-being. These two constructs of spirituality have an important role in supportive care and end of life care. The clinician should be sensitive to important end of life care decisions like, resuscitation, ventilator support, allowing for death in the clinical setting vs home, fears related to death and dying, and others. The decisions should be made in discussion with family, a peaceful environment should be created and have the loved ones close to the person, facilitate and encourage religious view points and doing things the family believes in providing good death. This could mean, avoiding the use of narcotics, avoiding excessive pain management, etc. It is important to provide calm in the environment, use of holy water, religious books, chanting prayers/mantras, sleeping in a certain position and others which in their religion is believed to provide good death. At this time of decision making, decisions of the patient and the family must be respected and followed even when against the judgement of the clinician, however, basic medical and bodily

needs must not be compromised. An ethically and morally challenging decision, should be thought, discussed and made with the family.

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Management Of Psychiatric Disorders in Patients with Endocrine Disorders.

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INTRODUCTION

There is an intimate and complex relationship between endocrine disorders and mental illness with increasing evidence of a bi-directional relationship between the two;e.g major depression is associated with the onset of insulin resistance and vice versa.[1]

Historically, Kraepelin had once proposed that dementia praecox was an endocrine disorder due to lack of thyroxine during the early part of the development which caused impairment in the maturation of behavior. [2]

Endocrine disorders like hypo and hyperthyroidism, diabetes mellitus are associated with prominent abnormalities in the mental status and mental illness. Those treatment can affect the endocrine status viz. Lithium in thyroid functions or second-generation antipsychotics affecting the blood sugars and precipitate the diabetes status. On this background, we will discuss the specific endocrine disorders associated with mental illness.

THYROID AND PSYCHIATRIC ILLNESS

The first confirmed relationship between thyroid disorder and psychiatric morbidity was reported way back in 1888 by the Committee of the Clinical Society of London.[3] Asher, roughly seven decades back, reported psychotic symptoms in 14 hypothyroid individuals and named the phenomenon '*myxedema madness'*.[4] This seminal case series laid the future ground for the definitive role of thyroid hormones (TH) in psychiatric disorders.[3]

Depression, anxiety, and cognitive difficulties are commonly reported neuropsychiatric symptoms (NPS) in thyroid disorders.[3] The symptoms of hypothyroidism imitate those of depression, whereas hyperthyroidism manifests as anxiety (up to 80 %) [3], emotional lability, dysphoria, depression (up to 70 %), and rarely mania.[4] Moreover, both hypothyroidism and hyperthyroidism are known to cause cognitive impairment citing which recommendation is placed for screening of thyroid dysfunction in cognitive disorders.[5] Interestingly, there is no consensus on population screening for thyroid diseases. But Garber and colleagues in the recent CPG have endorsed the need for case finding (thyroid disease) in psychiatric disorders. [6]

Hypothyroidism

Overt hypothyroidism (OH) is defined as an elevated serum thyroid-stimulating hormone (TSH) value and decreased serum thyroxine (T4) and/or tri-iodothyronine (T3) levels, with some clinical evidence of deficient TH action. The majority of affective disorders probands are euthyroid but 1 to 4% of these have OH and 4% to 40% have subclinical hypothyroidism (SCH).[4] Moreover, up to 52% of refractory depression, probands may have evidence of SCH.[4, 7] In a recent meta-analysis, odds of depression and anxiety in hypothyroidism were reported to be significantly high i.e. 3.56 and 2.32 respectively.[8] Additionally, up to 25 % of female rapid cycles have been found to have hypothyroidism.[5]

Neuropsychiatric symptoms in OH are ill-defined, non-specific, and *insidious* in onset. [3] Cognitive deficits like attention, concentration, and memory issues would start manifesting at early stages. With chronicity, the inability to perform daily chores and slow processing speed ensues. The striking feature is psychomotor retardation and increased fatigability. Specific difficulties in sustained mental exertion, comprehending complex questions, and learning new tasks are prevalent. Subsequent concern towards others and responsiveness is reduced. Along with these, depressive affect has been frequently reported.[5] In severe cases, illusions and visual hallucinations (VH) leading to paranoia are detected.[3] Psychosis in hypothyroidism has both admixtures of affective and schizophrenia.[3]

Differential diagnosis: Because of reduced responsiveness, slowing of thoughts (and actions), and attention problems, diagnosis may resemble depression. Depression in OH is colored with irritability and might run a chronic course. Psychosis in OH may be laden with confusion, persistent cognitive disturbances, and VH.

Treatment with levothyroxine (LT4) improves NPS, though the complete resolution of symptoms is not consistently achieved. Attainment of TSH levels in the physiological range generally would suffice to achieve adequate neuropsychiatric function. But despite adequate LT4 supplementation (up to 1.6mcg/kg/day [6]) some patients may still have residual NPS (e.g. long-standing dementia). Studies have attributed this residuum possibly to disease labeling effect or ascertainment bias. [4] There were initial reports of T3 *(not available in India)* augmentation of LT4 and improvement in residual NPS. [4] But subsequent controlled studies have shown inconsistent results and the combination needs further evidence.[9] McDermott [9] has suggested further evaluation for residual NPS (see table 1).

----------Insert table 1 here----------

Subclinical hypothyroidism is diagnosed when TSH levels are elevated with normal circulating free T4 and T3 concentrations. Frequent NPS (depression, anxiety, and cognition) in SCH have been reported at a young age while studies have been inconsistent regarding NPS prevalence.[4] Cardinal reasons for the inconsistencies are definitional issues (upper limit set for TSH) and age-related physiological rise. Importantly, it is pertinent to know the risk factors that would determine the progression from SCH to OH. Some of these factors including female gender, TSH >10 mIU/L, and presence of thyroid antibodies [10] emanates the need to treat with LT4 to prevent progression. But treatment outcomes of NPS with LT4 have been modest and inconsistent enough to draw any conclusion.[11]

Hyperthyroidism/Thyrotoxicosis

Hyperthyroidism is diagnosed when a patient has a low TSH value (<0.1 mIU/L) and an increased serum TH concentration, with some clinical evidence for excessive circulating TH action.[4] The most common etiology is Grave's disease.[3] The majority of psychiatric symptoms in hyperthyroidism resemble those (and mistaken for) of primary mental disorders and are due to secondary hyper-adrenergic.[5]

Neuropsychiatric symptoms (NPS) onset is usually *abrupt*.[3] The patient would routinely complain of nervousness, fatigue, restlessness, irritability, overactivity, emotional lability, and poor frustration tolerance. The associated heightened arousal often leads to distractibility and impairment of concentration. [3] Severe hyperthyroidism may exhibit delirium but is rarely encountered. Excessive circulating TH may *precipitate* impending psychiatric illnesses like anxiety or mania. An inflated sense of wellbeing akin to mania is often encountered in the early stages of hyperthyroidism. Depression, though more common in hypothyroidism manifests in prolonged hyperthyroidism due to noradrenergic exhaustion.[5] Interestingly, T4 levels tended to correlate with several anxiety symptoms but not for depression.[4] Intriguingly, in the elderly hyperthyroidism manifests as depression, lethargy, and mental slowing without the characteristic eye signs and is known as *'apathetic' hyperthyroidism*. Psychosis is uncommonly associated with hyperthyroidism and presents as an admixture of both affective and schizophrenia-like reactions.[3]

Differential diagnosis: An important differential diagnosis is anxiety states. Hyperthyroidism should be suspected if a clear history of sensitivity to heat or preference for cold is elicited, along with associated classical eye signs like lid lag, etc. Also, increase appetite in the face of persistent weight loss would be a key clinical differentiating feature from anxiety states where the appetite is reduced. Though stress precipitation is found in both conditions, it is more prevalent and exclusive in anxiety states.[3]

Treatment: The majority of hyperthyroid probands (50 % complete; 35 % partial) with NPS do respond if rendered euthyroid. [4,5] Occasionally, additional psychotropics are needed for residual symptoms. Beta-blockers would bring prompt relief even if euthyroidism is not restored. Propranolol (usually 60 to 80 mg) is preferred due to its effect on hyper-metabolism i.e. peripheral conversion of T4 to T3 [12] (kindly see treatment algorithm; figure 1).

----------Insert figure 1 here----------

Non-thyroidal illness and psychiatric disorders

Non-thyroidal illness is characterized by deranged thyroid function that occurs as a response to underlying systemic or acute psychiatric illness rather than an actual thyroid disease. Systemic medical illnesses may have low levels of T3, T4 and in more severe forms suppressed TSH.[13] Contrastingly, acute psychiatric illnesses may exhibit hyperthyroxinemia (elevated T4) in acute psychosis (and mood disorders) and elevated TSH in SUDs. Reasons emanating these hormonal changes are largely unknown.[13]

Thyroid hormones and refractory depression

Depression is not strongly correlated with an overt thyroid disorder but is associated with subtle irregularities like elevated TSH, altered circadian rhythm of TH, and blunted TSH response to TRH. Interestingly, TSH of the upper quartile range of normal is associated with recurrent, severe, and poorly responding depression phenotype. Importantly, TSH level may not always accurately reflects brain TH levels e.g., in D2 deiodinase deficient allelic polymorphisms (Thr92Ala polymorphism) there is the impaired conversion of T4 to T3 and resulting brain hypothyroidism. [4] Thus, T4 or T3 (more studied) has been added (to either augment or

accelerate the antidepressants response) in major depression even in absence of any biochemical thyroid dysfunction. [14] Clearly, in presence of SCH or OH, T4/T3 supplementation is warranted in case of refractory depression or rapid cycling states for clinical benefit.

Psychotropics and thyroid dysfunction

Lithium generally impedes the secretion of TH into blood circulation, decreases iodine trapping, and inhibits the synthesis of TH within the gland. The lithium-induced thyroid dysfunction varies substantially across studies reflecting both heterogeneous geography and varying definitions. Lithium-induced goiter prevalence varies from 2.5 – 50 %, is non-tender, and may occur within a few weeks.[15]

Lithium-induced OH and SCH have estimated prevalence rates of 8–19% and up to 23% respectively.[16] The presence of anti-thyroid antibodies, female gender, old age, and family history positive of thyroid dysfunction are the most important risk factors for lithium-induced hypothyroidism (LiI-Hypo).[16] Studies have found a mean weighted difference of TSH 4.00 mIU/L on lithium therapy than those without over the mean 70 months.[15] Given the substantial morbidity, at least TSH assessments are recommended at baseline and thereafter at least biannually or depending upon clinical discretion.[16] Whether the dose and length of lithium therapy increase the incidence of hypothyroidism is unclear. Importantly, it is pertinent to remember that *hypothyroidism never justifies lithium discontinuation*.[16] Thyroid supplementation is required in OH and SCH if TSH >10 mIU/L [17] (kindly see treatment algorithm; figure 1). Interestingly, the case if TH is stopped after lithium is discontinued, re-emergence of hypothyroidism is reported. Therefore, lithium may accelerate the underlying thyroiditis or SCH. [16, 17]

As per the retrospective data, lithium may counterintuitively result in hyperthyroidism years after the therapy. Lithium-induced hyperthyroidism ((LiI-Hyper) is more common in females and is short-lived painless thyroiditis. Treatment principles remain identical to those treating hyperthyroidism and a course of antithyroid drugs like carbimazole shall be initiated [15] (kindly see treatment algorithm; figure 1). Many patients may go on to develop hypothyroidism.[15] Interestingly, lithium carbonate is used as a short-lived add-on therapy to radioiodine in the treatment of hyperthyroidism.[18] Lithium may rarely result in an increase in blood calcium (by 10 %) and parathyroid hormone (PTH) levels lending guidelines to make it prudent to assess calcium also along with TFT.[16]

Other mood stabilizers: Carbamazepine (CBZ) may reduce the levels of free T4 within 2 months without inducing clinical hypothyroidism. This TH suppression is usually reversible and doesn't warrant precautious monitoring. But valproate and CBZ combination warrant precautious monitoring of TH citing suppression of free T4 levels and increase of TSH.[17]

Other psychotropics: Tricyclic-antidepressants (TCA) and phenothiazines via formation of drug-iodide complexes may induce clinical hypothyroid state and thereby would require regular monitoring of thyroid function. [17] Moreover, among antipsychotics, those with a higher propensity to increase prolactin might derange TFT more than those without. Euthyroid

hyperthyroxinemia (high T4 but normal TSH) has been reported with methadone and stimulant use. [13, 17] Benzodiazepine doesn't seem to affect thyroid function parameters.

HYPERPARATHYROIDISM

Hyperparathyroidism is prevalent in around .1 % of the population and is more in aged females. Primary hyperparathyroidism (PHPT) is characterized by the presence of elevated PTH levels, calcium levels, and hypophosphatemia. [3] Classical symptoms of hypercalcemia like fatigue, lethargy, or loss of appetite may resemble primary psychiatric morbidity. Onset may be insidious and gradually progress to coma. Hyperparathyroidism may give rise to abdominal cramps ("moans"), bone disease ("bones"), and renal stones ("stones"). Unlike earlier times, early recognition of hyperparathyroidism is currently more feasible due to routine biochemical screening. [3] Apart from reasons like head and neck radiation therapy, an important plausible etiology is lithium therapy. Lithium may stimulate PTH secretion and result in hypercalcemia in around 10 % of cases. [16] Though fortunately lithium-induced hypercalcemia is associated with a lower incidence of renal stones. Importantly, hypercalcemia shall be considered as a differential in lithium-treated probands with atypical psychopathology or non-response to treatment. [19]

NPS in hyperparathyroidism accounts is largely cited by case reports and case series. The most frequent psychopathology reported is depression (up to 62 %) and anxiety (up to 53 %). Cognitive symptoms of ensuing depression are marked but only in the elderly population. The presence of apathy, irritability (up to 51 %), or fatigue ("psychiatric overtones") should be alerting and has been associated with mild to moderate hypercalcemia. [20] Overt delirium and coma have been reported when calcium levels are markedly elevated i.e. above 14 mg/dl. Psychosis is a rarely described phenotype. Recently, the major neurocognitive syndrome has been reported to be associated (though weakly) with long-lasting hyperparathyroidism. [21] With chronicity, seclusion and withdrawn behavior ensue. [19]

Most studies have found improvement in NPS post successful surgical treatment unless the disease chronicity has set in. However, the measured improvement of NPS specifically in mild PHPT cases has been of uncertain clinical significance. Therefore, in overt hypercalcemic hyperparathyroidism with NPS, surgical removal of parathyroid glands is a definitive and straightforward treatment option. But in probands with mild PHPT with NPS, surgical treatment is not recommended option as per the international workshop on PHPT. [20]

HYPOPARATHYROIDISM

The most common cause of hypoparathyroidism is iatrogenic i.e. either removal or interference with the blood supply of parathyroids during neck surgeries. Resulting hypocalcemia does present with neuromuscular irritability, cramps, paresthesias, facial grimacing, and seizures. These may again resemble a neuropsychiatric condition. [19]

NPS is present in around half of the probands who developed hyperparathyroidism after surgery and may even be higher in idiopathic ones. [3] Delirium is expected in the post-surgery period as a complication due to the associated biochemical disturbances. In idiopathic hypoparathyroidism, anxiety disorder, emotional lability, and depressive symptomatology

have been described. Probands have been reported to suffer from irritability, socially awkward behavior, and nervousness. Intriguingly, descriptions of the psychotic symptoms in clear consciousness have been uncommon. Cognitive deficits (subtle and major neurocognitive) have been reported but severity increases with chronicity of the endocrine disease. Basal ganglia calcifications are common in hypoparathyroidism and are related to poor quality of life. NPS developing in the background of intracranial calcifications are reported to be more refractory. Hypoparathyroidism is frequently associated with velocardiofacial syndrome (VCF; 22q.11.2 deletion syndrome). VCF syndrome would present as schizophrenia and mood disorder in adults. Hypoparathyroidism pathogenesis is mainly due to hypocalcemia. NPS symptoms such as depression and anxiety would appear episodically in "partial parathyroid insufficiency" due to frequent instances of calcium deprivation. Because anxiety can provoke hyperventilation, tetany can be precipitated in hypoparathyroidism patients. [19]

Response to correction of serum biochemistry is usually rewarding in non-chronic hypoparathyroidism cases. Depression and anxiety symptoms would remit in the majority of cases. Short-term benzodiazepines can be considered if the anxiety is debilitating. Post-surgical delirium would resolve spontaneously. Almost half of the cases with cognitive impairment would improve with serum biochemistry correction barring those with intracranial calcification or long-standing cases. There are some reports of enhanced sensitivity to neuroleptics in hypoparathyroidism. [19]

Largely, organic psychiatry syndromes due to thyroid and parathyroid disorders require merely endocrine treatment unless the NPS persists after 4 weeks of adequate treatment or is severe in intensity. NPS in thyroid and parathyroid disorders and their clinical relevance are described in table 2.

----------Insert table 2 here----------

DIABETES AND PSYCHIATRIC ILLNESS

Introduction

Diabetes mellitus is a chronic medical condition that has hazardous consequences not only on the various organ systems of the body but also affects the emotional wellbeing of patients.[22] There is an increasing trend of the disorder seen globally with nearly 77 million cases in the adult population of India. The prevalence is also showing an increasing trend among the urban [19%] and rural [15%] areas of India for both diabetes and pre-diabetes. [23] There are about 422 million people worldwide having diabetes, with the majority living in low-and middle-income countries. [22] In India, the number of people with diabetes is expected to rise from 77 million in 2019 to 101 million in 2030 to 134 million in 2045. India also ranks second in the number of people with undiagnosed diabetes: China (65.2 million); India (43.9 million); and the United States (11.8 million).[23]

This is therefore a source of concern as the socioeconomic costs of diabetes are escalating and it is causing a burden on health care resources and infrastructure to cater to the diabetes-related

complications, repeated admissions, emergency care, renal failure, amputations, etc. [24] All this has caused an increase in psychological and social problems with nearly one-third of the patients expressing inability to self-manage their diabetes. An interrelationship between diabetes and mental illness has already been studied where the psychological status of the patients could impact the need for glycemic control, and the further development of complications, disability, or mortality associated with diabetes. Another area of concern is the increased prevalence of non-insulin-dependent diabetes mellitus due to metabolic side effects caused by psychotropics given to psychiatric patients. [24] There is enough literature examining the relationship between diabetes and psychiatric illness seen in both Type 1 and Type 2 diabetic patients (see figure 2).

----------Insert figure 2 here----------

Stress and Diabetes

The impact of stress directly on the physiology of glucose metabolism is not very clear, though studies have shown that glycemic control was poor in those diabetics who reported stress.[25]

Depression and Diabetes

There are several views as to whether depression is the cause or effect of diabetes. The exact direction of the association has not been determined through several researchers who have reported both. Lustman et al reported that the relationship was reciprocal with hyperglycemia either being provoked by depression or contributing to the exacerbation of depression.[26] Several meta-analytic studies have reported the rates of depression in diabetes to increase two-fold or threefold as compared to the general population.[27] Lustman et al reported a strong association between HbA1C values and depression.[26]

There is also a lot of inconsistency in what methodological parameters were used to diagnose the depressive symptoms. Researchers have pointed out that the mere presence of symptoms may not constitute a depressive disorder as several studies use scales like PHQ without using clinical interviews. This probably could result in a high prevalence as compared to the general population. Lloyd et al in their INTERPRET-DD study in 14 countries revealed the prevalence of current major depressive disorder as per MINI to be 10.6% but a higher number of moderate to severe depressive symptoms as per PHQ were reported by 17% of the patients. Golden et al reported minor depression in 13% of the diabetic patients suggesting that other depressive disorders are equally prevalent. [28]
Symptoms of depression-like decreased motivation and energy decreased interest and hopelessness could interfere with adherence to anti-diabetic medication leading to poor glycemic control and diabetes-related complications. [24]

Both lifestyle factors and biological mechanisms could be responsible for depressive symptoms in diabetics. Insulin resistance is now recognized as an important regulator of mood and causes an increase in cytokines which results in a pro-inflammatory state. Inflammation has also been

linked to depressive symptoms and there is a poor response to antidepressants in those patients who have elevated inflammatory markers.[24] This has also led to the hypothesis that depression could lead to diabetes because depression affects the hypothalamic-pituitary axis resulting in increased cortisol production and other counter-regulatory hormones leading to insulin resistance.[24] Other risk factors in depressed patients include decreased physical activity, eating high caloric fatty foods, indulging in smoking or drinking which again put them at risk for diabetes (see figure 3).

----------Insert figure 3 here----------

Assessment of patients

Every patient with diabetes and depression should be evaluated for:

----------Insert figure 4 here----------

Management of depression in diabetes

Management of depression can be done with a holistic approach (see figure 5):

----------Insert figure 5 here----------

Use of antidepressants (see table 3)

- All antidepressants have a favorable outcome on depressive symptoms which then improves self-care behavior resulting in improved glycemic control. [24,29]
- All groups of antidepressants can be given safely in diabetes.
- Both SSRIs and Bupropion improve the depressive symptoms in diabetics; they also stabilize or lower glucose levels.
- Tricyclic antidepressants like nortriptyline and imipramine could increase glucose levels and hence regular glycemic monitoring is required.

----------Insert table 3 here----------

Use of CBT for treatment of depression and improving glycemic control

- Mild depressive cases do well with CBT. [30,31]
- CBT can improve diabetes-related distress
- CBT improved depression than diabetes-related distress in some studies as interventions were not tailored in problem areas of self-care [30,31]
- Short-term reduction in mean HbA1c due to CBT was seen
- CBT can help in changing diabetes self-care behaviors by changing the negative beliefs about the illness which can then result in better glycemic control.
- Short term benefits > long term effects

Use of internet guided self-help interventions

Some studies have reported the efficacy of using internet-guided measures which give a short-term benefit for depression and diabetes and can be done easily by integrating into the diabetes self-care program.[32]

Lifestyle modifications

Healthy eating, regular exercise, yoga, relation, and breathing techniques go a long way in improving both physical and mental outcomes.

Anxiety and Diabetes

Anxiety disorders are quite prevalent in type 2 diabetes and can also lead to poor diabetes-related self-care, glycemic control, and an increase in diabetes-related complications. The most prevalent anxiety disorders in diabetes include generalized anxiety and panic disorders with a higher prevalence of subsyndromal anxiety.[24,33] Rehnberg in their review of 15 correlational studies found an association between anxiety symptoms and poor health like glycemic control, fear of hypoglycemia, worry about hypoglycemia, family conflict, depressive symptoms, blood glucose monitoring, and quality of life.[34] Three studies also looked at interventions to reduce anxiety in type-1 diabetes like participation in a summer camp for a week, which improved attitude towards diabetes and reduced trait anxiety, CBT which included cognitive restructuring and problem-solving skills whereas continuous glucose monitoring did not affect anxiety. [34] Early management of the anxiety by using either pharmacological and/or nonpharmacological therapies would help in improving the disease-related burden and complications.

Bipolar disorder and diabetes

A prevalence of 10-26 % of diabetes has been seen in bipolar disorders more commonly due to the weight gain due to psychotropics, obesity, shared genetic risk, psychiatric and medical comorbidities, etc.[35] Reducing the risk with proper monitoring of patients on psychotropics and lifestyle modifications needs to be followed. [24]

Schizophrenia and diabetes

Several studies have pointed out an increased risk of developing diabetes in patients with schizophrenia. The most common risk factors include sedentary lifestyles, associated nicotine use, increased appetite, and eating high carbohydrate caloric food, and metabolic side effects of atypical antipsychotics which cause hyperlipidemia, glucose intolerance, insulin resistance, and weight gain. As atypical antipsychotics are usually preferred due to their reduced extrapyramidal side effects, there is a surge in their use which has resulted in metabolic syndrome. The following should be done when doing management of schizophrenia and diabetes [24,36] (see table 4):

----------Insert table 4 here----------

Eating disorders and Diabetes

Researchers have reported that the aggressive management for diabetes control often results in weight gain, which then becomes difficult to lose. This often results in undue weight watching, attention to food portions, blood sugars which may trigger health consciousness more in women with type-1 diabetes which may then cause eating disorders.[24] Body image concerns and a phenomenon called insulin manipulation are seen in these patients where women with type-1 diabetes omit or reduce insulin doses which are akin to caloric purging and a symptom of eating disorder-specific to type-1 diabetes. This also places them at a higher risk for ketoacidosis and retinopathy with higher HbA1C levels. The prevalence of eating disorders in adolescents with type 1 diabetes is around 7% and is also known as *diabulimia.*[37]

Many times, as these patients may not show self-induced vomiting or laxative abuse, their eating disorders often go undiagnosed. Dietary restriction, binge eating is common but classical anorexia nervosa is rare. Obesity being a risk factor for type-2 diabetics, recurrent binge eating is often seen. [24] Management of diabetic patients with eating disorders should be done as follows (see table 5):

----------Insert table 5 here----------

Sexual Dysfunction and Diabetes

Sexual dysfunctions occur in diabetic males due to increasing age, duration of diabetes, and diabetic complications. The various sexual dysfunctions in males include primarily erectile dysfunction (ED), loss of sexual interest, and ejaculatory disturbances.[38] Women with type 1 and type 2 diabetes reported loss of libido and arousal with reduced vaginal lubrication. [39]

For the assessment and management of these patients kindly refer to the chapter on Psychosexual health and sexual medicine in CLP.

Cognitive functioning and Diabetes

Hyper/hypoglycemia in children or adolescents with type 1 diabetes have [40]:

- learning difficulties
- reduced speed of processing
- attention deficits
- short term memory difficulties

Hence children should be regularly assessed for the same and parents counseled.

Similarly in adults with type 2 diabetes a long time exposure to chronic hyperglycemia, uncontrolled sugars, and micro and macrovascular changes in the brain increases the risk of cognitive decline and dementia.[24]

Regular monitoring of the sugars to prevent ischemic changes is the only preventive strategy.

It is recommended that to rule out complications, all patients of type 2 diabetes should have an annual:

- complete physical examination
- foot examination

- eye check-up

METABOLIC SYNDROME

Metabolic syndrome is not a disease but a condition associated with cardio-metabolic problems occurring worldwide due to lifestyle changes along with genetic vulnerability. It is now a major public health concern due to increased mortality due to its risk for cardiac diseases. People with mental illnesses like schizophrenia, bipolar disorder, and depressive disorders are at a higher risk for developing metabolic syndrome as compared to the general population. [41, 42]
Metabolic syndrome (MetS) refers to the presence of cardio-metabolic conditions like abdominal obesity, glucose intolerance or insulin resistance, dyslipidemia [higher levels of triglycerides and decreased high-density lipoprotein (HDL); cholesterol levels] and hypertension (see figure 5). [41, 42]

----------Insert figure 6 here----------

The risk posed by psychotropics in the causation of MetS is inconsistent whether a trial is given with a single drug or polypharmacy is done or reduction of weight with the use of aripiprazole is considered.

----------Insert table 6 here----------

Management of metabolic syndrome

Management of metabolic syndrome includes lifestyle changes to prevent health problems like a heart attack or stroke (see Figure 7).

----------Insert figure 7 here----------

HYPERPROLACTINEMIA AND PSYCHIATRIC ILLNESS

Psychological stressors associated with hyperprolactinemia are one of the explanations for hyperprolactinemia in drug naïve patients. [43,44,45] Galactorrhoea is commoner in females with hyperprolactinemia in comparison to males [46] and is found in almost 10-20% of females treated with first-generation antipsychotics. [47]

Clinical presentation with hyperprolactinemia

Serum prolactin level of 99.6 ng/mL is associated with hypogonadism, amenorrhea, and galactorrhoea. A level of 50.8 – 74.7 ng/mL is associated with oligomenorrhea. A level of 30.9 – 49.8 ng/mL is associated with reduced libido. The risk of osteoporosis and malignancy in hyperprolactinemia is associated with severe mental illness. Patients with schizophrenia are 2-4 times more likely to have osteoporosis and at 70% increased risk of fractures in comparison

to the general population. [48] Hyperprolactinemia is associated with an increased risk of malignancy in females especially breast carcinoma. [49]

Management of antipsychotic-induced hyperprolactinemia

- Pre-treatment prolactin level of more than 1000 IU/L needs further evaluation before starting the treatment (see flowchart; figure 8).
- Hyperprolactinemia in asymptomatic patients with serum level of less than 2500 IU/L does not require any further investigation or treatment
- Serum prolactin level of more than 2500 IU/L requires a low dose of bromocriptine of cabergoline and further endocrine referral

---------- Insert figure 8 here----------

STEROIDS AND PSYCHOSIS

Steroid-induced psychosis is categorized as the substance or medication-induced psychosis in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. To diagnose steroid-induced psychosis operational criteria have to be met. First, the patient must have exposure to a medication capable of producing symptoms such as delusions or hallucinations. The psychopathology cannot be explained by other non–medication-induced psychotic disorders, and importantly it shall not occur exclusively during a delirium. Lastly, it must cause clinically significant distress or functional impairment.

The incidence of severe neuropsychiatric symptoms (including psychosis) due to steroids has been estimated to be around 6 %. [50] Though the effects of steroids are unpredictable, the administered dose within 2 weeks is the most significant risk factor for the development of neuropsychiatric symptoms. Interestingly symptoms can occur any time and even after cessation of therapy. The pathophysiology is poorly understood but the preferential selection of glucocorticoids over mineralocorticoids stimulation is said to lead to emotional changes.

Management: Prevention hinges on using lower dosages and not prolonging the duration of the treatment. Treatment is reassuring with reduction or stopping of steroids and addition of antipsychotics. Haloperidol is the most frequent antipsychotic used. [51]

CONCLUSION

This CPG looks at the most common endocrine disorders seen in practice and associated psychiatric comorbidities. Understanding the connection between hormones and human behavior and liaison by the treating physicians would entail a better quality of life and medical outcomes for the patient. The impact of stress on the immune response and the hypothalamic-pituitary-adrenal (HPA) axis is important to address in consultation-liaison. We have provided an approach to the management of the psychiatric conditions associated with endocrine dysfunction like depression, anxiety, cognitive dysfunction, psychosis, delirium. The patient with endocrine dysfunction may either present with psychiatric symptoms and the endocrine dysfunction may often go undiagnosed or psychiatric symptoms may occur anytime during illness. An early diagnosis and appropriate referral may go a long way in improving the health-

related outcomes and coping of the patient. Further reading for specific disorders is suggested in references, as it would otherwise be very exhaustive.

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Table 1: Further work up of residual Neuropsychiatric symptoms (NPS) in overt hypothyroidism [9]

Thorough physical examination
Obstructive sleep apnoea screening
Blood biochemistry including metabolic panel
Vitamin D levels
Thyroid antibodies
Exercise
Dietary changes
Sleep hygiene
Change of brand of levothyroxine

Table 2: Neuropsychiatric symptoms (NPS) in thyroid and parathyroid disorders [19]

NPS	Hypothyroidism	Hyperthyroidism	Hypoparathyroidism	Hyperparathyroidism
Onset	Insidious	Abrupt	Post operative	Insidious
Depression	++	++/30 to 70 %	+	++/ upto 62 %
Apathy	+	Apathetic hyperthyroidism		+
Anxiety	+	+++	+	++/ upto 53 %
Delirium	+	+	++	++/ 2 to 5 %
Cognitive decline	+++ Cretinism	++	+	++
MNCD	++	+/-	+/-	+
Others	Slowing/ Psychomotor retardation/ Mania (treatment induced)	Overactivity/ Inflated sense of well-being/Irritability	Social withdrawal/ Neurotic behaviour/ Poor quality of life if basal ganglia calcifications	irritability (upto 51 %) or fatigue
MNCD: Major Neurocognitive disorder; +/+++: Clinical relevance				

Table 3: Choice of Antidepressant in diabetes

Choice of Antidepressant Medication in depression with diabetes	**Effect on diabetes**
SSRIs • **Fluoxetine** • **Sertraline** • **Paroxetine** • **Escitalopram**	**All SSRIs preferred among antidepressants due to their efficacy, lower side effect profile**. **Fluoxetine** was much better in causing hypoglycemia, weight loss, decreased body fat and better glycemic control as compared to the other SSRIs. **Can be first drug of choice.**
Bupropion	Reduction in BMI, body fat and HbA1c levels **Can be considered**
TCAs • **Nortriptyline** • **Imipramine** • **Amitrytiline**	Can cause hyperglycemic effect, no change in HbA1c levels Can cause hyperglycemic effects Can cause weight gain, inconclusive effects on glucose metabolism **Use of TCAs requires regular glucose monitoring**
SNRI • **Venlaflaxine** • **Duloxetine** • **Mirtazepine**	Inconclusive evidence on glucose metabolism Can cause weight loss Regulates body weight, safe in stable diabetic patients but interferes with glucose metabolism
SARI • **Trazodone**	No evidence on glycemic control
Choice of Antidepressant Medication in depression with diabetes	Effect on diabetes
SSRIs • **Fluoxetine** • **Sertraline** • **Paroxetine** • **Escitalopram**	**All SSRIs preferred among antidepressants due to their efficacy, lower side effect profile**. **Fluoxetine** was much better in causing hypoglycemia, weight loss, decreased body fat and better glycemic control as compared to the other SSRIs. **Can be first drug of choice.**
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SNRI • **Venlaflaxine** • **Duloxetine** • **Mirtazepine**	 Inconclusive evidence on glucose metabolism Can cause weight loss Regulates body weight, safe in stable diabetic patients but interferes with glucose metabolism
SARI • **Trazodone**	 No evidence on glycemic control

TABLE 4: Management of diabetes in schizophrenia

Before initiation of antipsychotic medication check for glucose intolerance
Do both fasting and postprandial assessment; HBA1C if sugars deranged
Evaluate for history of: • Gestational diabetes • Obesity • Family history of diabetes
Check for hyperlipidemia
The **choice of antipsychotic with a lower propensity for weight gain** and metabolic alterations includes**:** ➢ **ziprasidone** ➢ **lurasidone** The other antipsychotics as per their effect on glucose metabolism, lipid dysregulation**,** weight gain in **descending order** include**:** ➢ aripriprazole ➢ risperidone ➢ amisulpride ➢ quetiapine ➢ paliperidone ➢ asenapine ➢ haloperidol
Antipsychotics to be avoided in patients with risk factors and causing weight gain **:** ➢ **Olanzapine** ➢ **Clozapine** ➢ **Sertindole**
No current consensus on monitoring of glucose and lipids when atypical antipsychotics are prescribed
Use of pre/probiotics in diet can reduce gut dysbiosis and metabolic syndrome

TABLE 5: Management of diabetes in eating disorders

A multidisciplinary approach with an endocrinologist/ diabetologist, trained nutritionist with diabetes and eating disorder experience, mental health professional and counselor to deal with the problem
Medical stabilization of diabetes
Increasing dose of insulin
Increasing food intake
Flexible meal plan
Regular eating routine
Regular glucose monitoring
Evaluation of comorbid psychopathology
Use of CBT to address issues of insulin omission and manipulation
Use of antidepressants

Table 6: Risk of metabolic syndrome with psychotropics (42)

Increased risk for MetS with type of Antipsychotics ➢ **Clozapine (47.2%)** ➢ **Quietiapine (37.3%)** ➢ **Olanzapine (36. 2%)**
Lowest risk for MetS with type of Antipsychotics ➢ **Aripriprazole (19.4%)** ➢ **Amisulpiride (22.8%)**
Risk for MetS with antidepressants is still unclear. Some studies postulate that antidepressants with H1 receptor antagonist function can be responsible for causation of MetS. ➢ **Mirtazepine, paroxetine,TCAs cause weight gain/obesity** ➢ **SNRIs, bupropion,TCAs may cause hypertension** ➢ **TCAs increase risk for diabetes**
Adding antipsychotic medication for augmenting action of antidepressants can also be a risk factor.
Among mood stabilizers: ➢ **Lithium and Valproate may cause weight gain/obesity and dyslipidemia** ➢ **Valproate has greater risk for diabetes as compared to lithium, lamotrigine,oxcarbazepine** ➢ **Lamotrigine/topiramate have no effect on obesity**

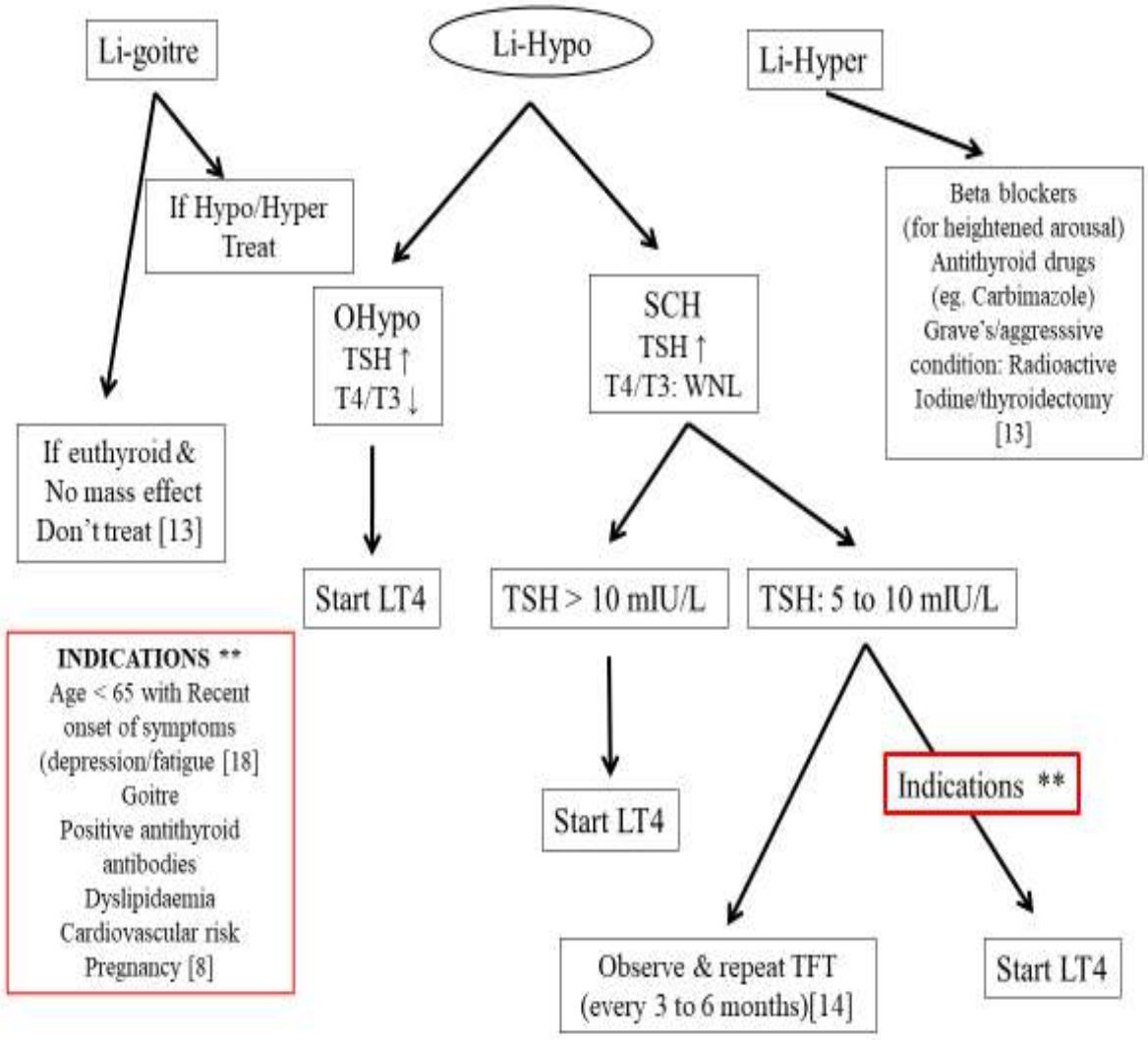
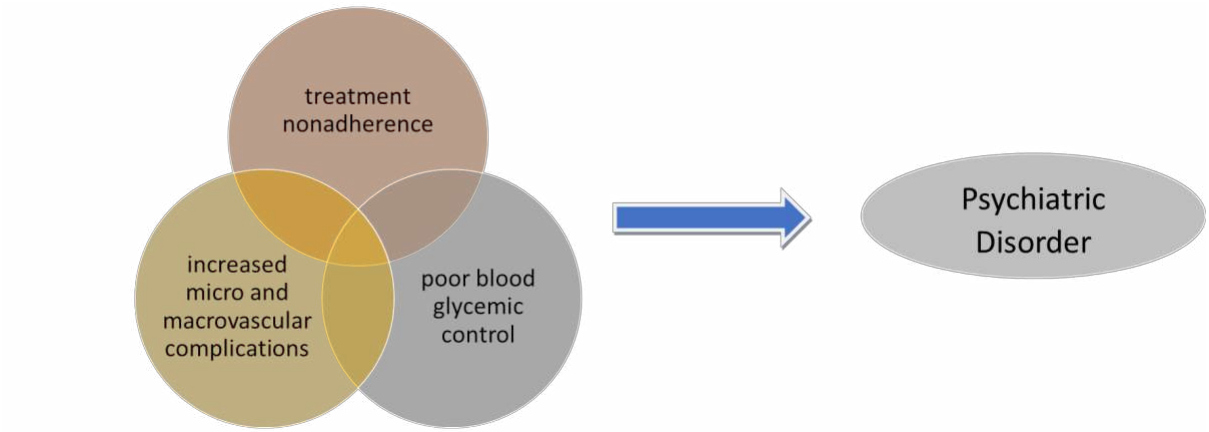


Fig 1: **Treatment algorithm** for lithium induced thyroid dysfunction. Li: Lithium; Hypo: Hypothyroidism; Hyper: Hyperthyroidism; OHypo: Overt Hypothyroidism; OHyper: Overt Hyperthyroidism; SCH: Subclinical Hypothyroidism; TSH: Thyroid stimulation Hormone; T4: Thyroxin; T3: Tri-iodothyronin; LT4: Levothyroxine; WNL: Within Normal Limits

Figure 2: Diabetes & Psychiatric disorders



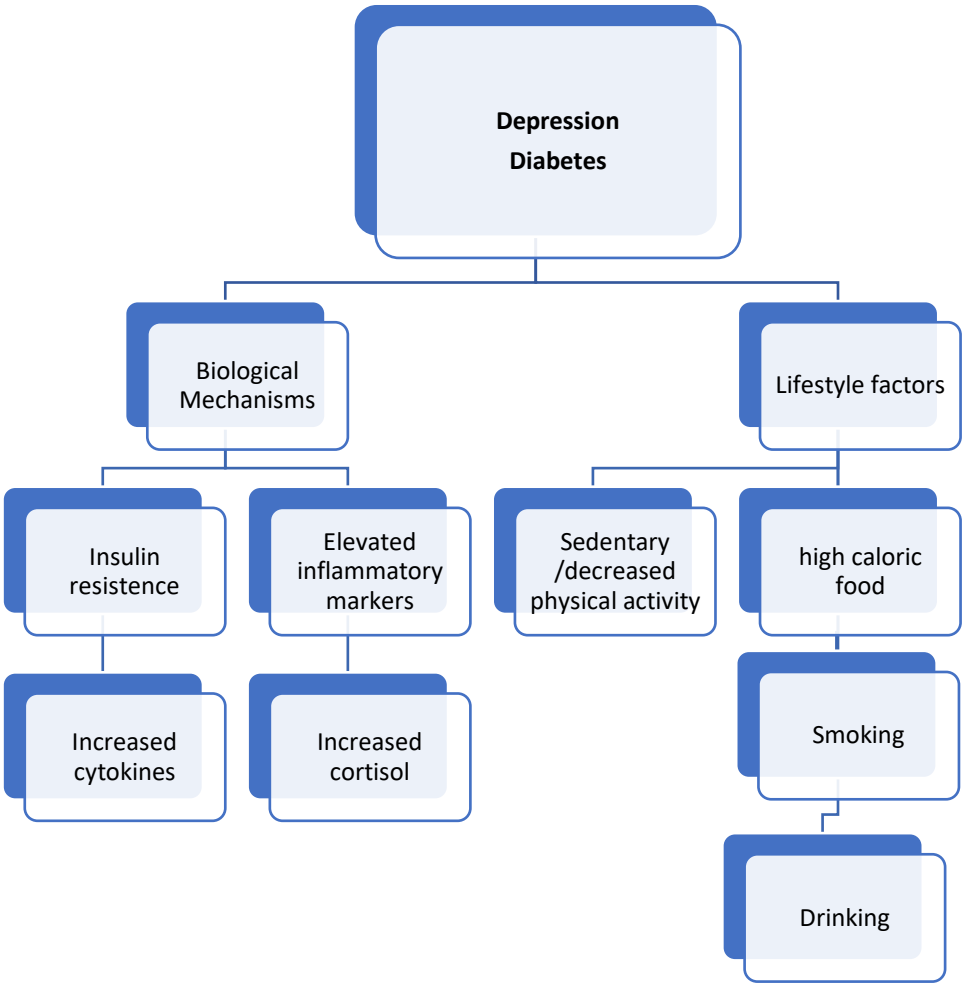


Figure 3: Depression & Diabetes: Mechanisms and risk factors

Detailed psychiatric history
Risk factors, family history
General Examination
BMI, weight
Blood investigations : Blood sugar fasting & post prandial, HbA1C
Screening for cardiac, renal and ophthalmic complications
Use of scales for evaluation of depressive symptoms: BDI, PHQ-9
Diabetes specific measures like Quality of life to assess for burden of self care
Evaluate for cognitive decline due to the chronic ischemic changes
MRI brain if needed

Figure 4: Parameters to evaluate in depression and diabetes

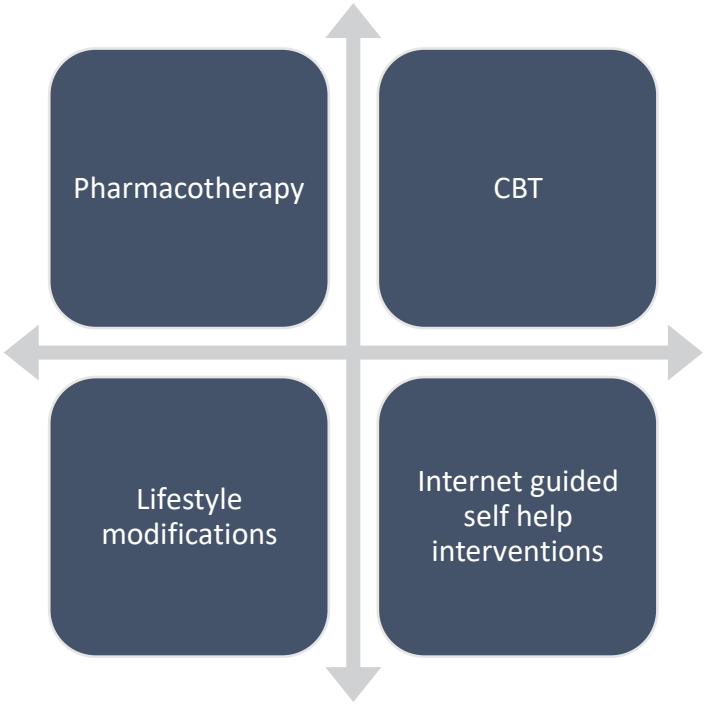


Figure 5: Treatment arms in depression and diabetes

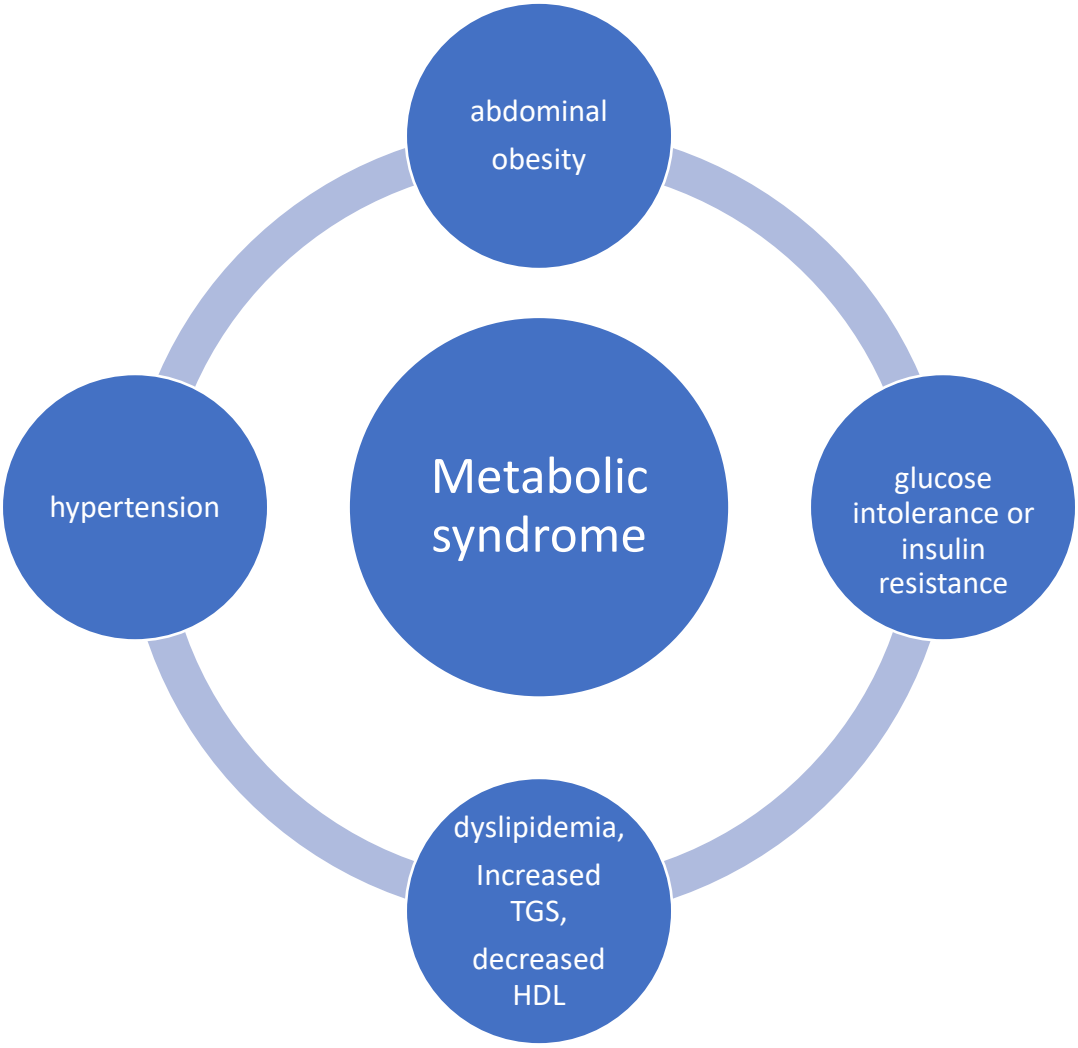


Figure 6: Signs of Metabolic syndrome

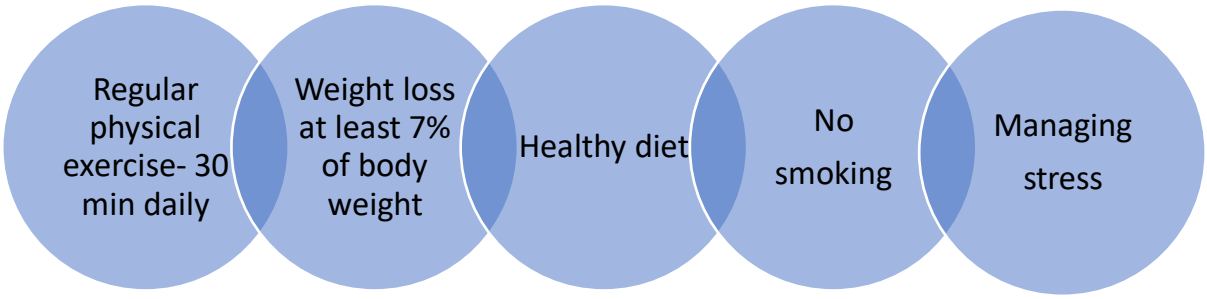
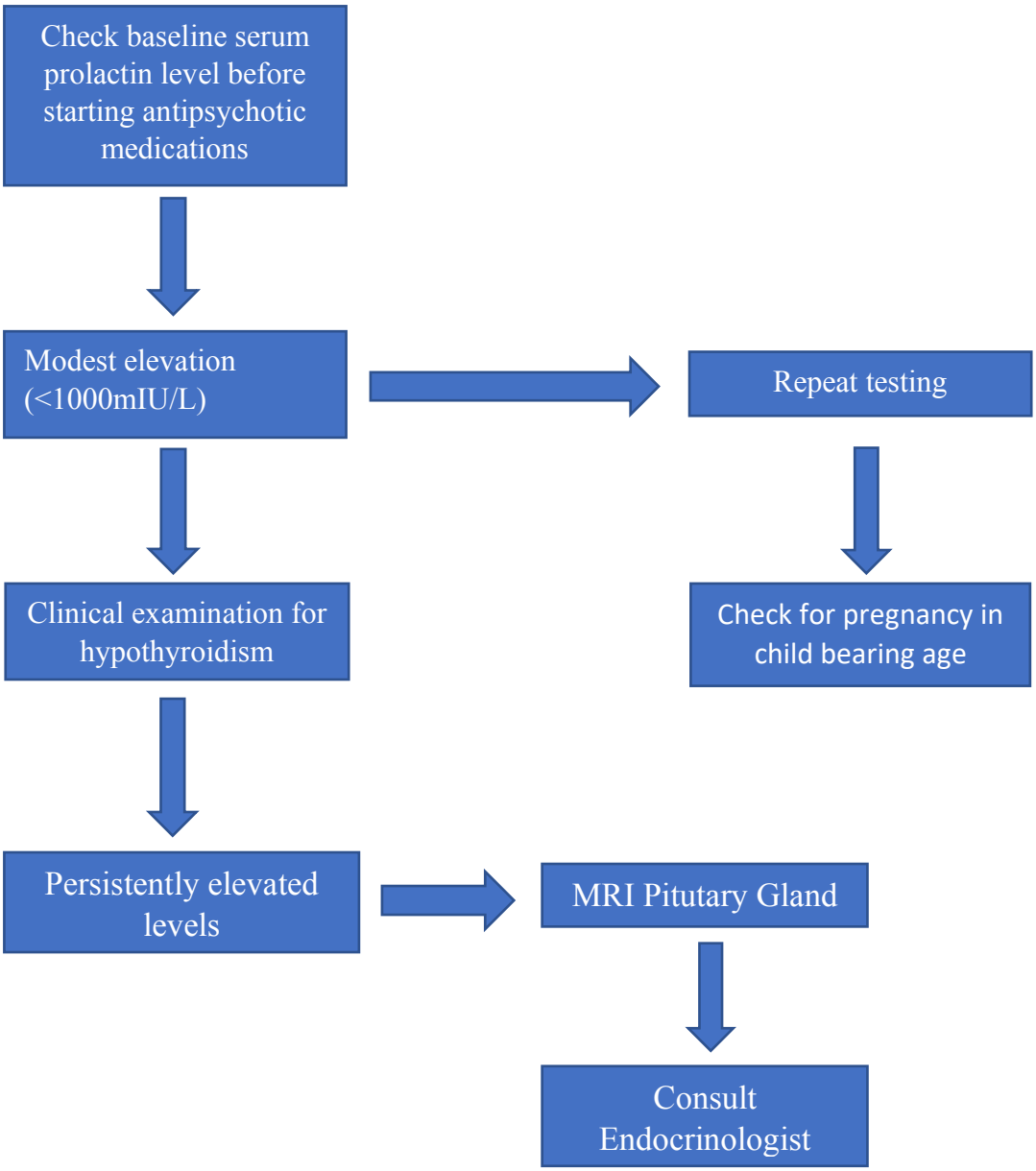


Figure 7: Management of metabolic syndrome

Figure 8: Flow chart of clinical evalution of hyperprolactinemia



Management of psychiatric disorders during the perinatal period

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Introduction

The psychiatrist working in a general hospital psychiatric unit (GHPU) has several opportunities for consultation-liaison work with the obstetrician. There is a bidirectional relationship between psychiatry and obstetrics. While on one hand, the improved management of psychiatric illness is helping many more women with mental illness embrace motherhood; on the other hand, psychiatrists often receive referrals for the evaluation of women undergoing treatment for infertility or Assisted Reproductive Techniques (ART) or antenatal and postnatal care. From the obstetrician's point of view, the major contributors to maternal mortality in the past were obstetric complications such as haemorrhage and medical disorders complicating pregnancy such as diabetes mellitus and hypertension. However, with improved obstetric care protocols and a significant reduction of maternal mortality rates due to obstetric and medical diseases, maternal mental health has come to the fore as one of the major contributors to morbidity and mortality.

A psychiatrist may receive a referral for consultation in three broad situations: -
(i) either as an out-patient referral from the antenatal or postnatal clinic of obstetrics;
(ii) in the obstetric in-patient or labour room; or
(iii) from the obstetric emergency services.
This article is organised as follows:
First, we would like to give a broad overview of the various conditions that may be seen in the context of the perinatal period, including the medical disorders that can lead to these presentations and the suggested investigations.
Second, we present a format for clinical assessment.
Third is a note on the general principles of management in the perinatal setting, including a note on the risk-benefit analysis of medications and management planning.
Fourth is a section on management of individual disorders in the perinatal period.
Finally, we cover other conditions such as management of suicidal risk, agitation, the use of Electroconvulsive Therapy (ECT) and repetitive Transcranial Magnetic Stimulation and the future role of mother-baby units in general hospital psychiatry.

Overview of psychological conditions in the perinatal period

Pre-conception: In the pre-conception stage, there are broadly three groups of patients who may be referred for evaluation: (i) Patients undergoing treatment for infertility or assisted reproductive techniques (ART) who may be referred for psychological issues such as stress, anxiety and depression; (ii) Patients with previous traumatic experiences during pregnancy and childbirth; (iii) those with pre-existing psychiatric illness.

Patients who are undergoing treatment for infertility and those with previous traumatic experiences during childbirth, such as injuries during labour, disrespectful care during labour, stillbirth or requirement for emergency interventions including Caesarean section may be at risk for psychological morbidity such as depression and anxiety. Patients with pre-existing psychiatric illnesses may need a review of their clinical condition and decision on continuation, modification or discontinuation of medication will have to be taken.

During pregnancy referrals may be received for women with new onset of a psychiatric condition, pre-existing mental illness or for psychological distress caused by psychosocial factors such as marital discord, domestic violence or substance use in spouse.

Events around **childbirth**, such as stillbirth can lead to grief. There may be psychological distress related to gender of the infant. Medical illness in the infant and separation of mother and infant due to NICU admission may also lead to psychological distress including anxiety, anticipatory grief.

In the postpartum period, disorders of mother-infant bonding may be there. Mood related changes may present as postpartum blues or postpartum depression. Postpartum psychosis is a particularly severe form of behavioural disturbance that may be seen in the postpartum period.

Table 1 & 2 present an overview of the various conditions seen in the perinatal period.

Table 1: Overview of perinatal psychiatric conditions for which consultation may be sought

Pre-Conception		
Context or Risk factors	**Psychosocial factors**	**Psychiatric conditions**
Infertility & Assisted Reproductive techniques (ART)	Psychological effects of medications or treatment Excessive worries Marital discord	Anxiety Depression
Trauma during childbirth / Disrespectful care / Perinatal loss / Emergency Caesarean section	Tokophobia – fear of pregnancy & childbirth Excessive worries about pregnancy and foetal health	Anxiety Post-Traumatic Stress Disorder (PTSD) Grief Mother-Infant Bonding disorders
Women with pre-existing severe mental illness (SMI) such as schizophrenia, bipolar disorder or recurrent depressive disorders, planning for pregnancy	Fear of teratogenic or other adverse effects of medications Pressure from family to stop prophylactic medications Inability to follow-up regularly	High risk of recurrence (60-80%) of severe mental illness (SMI) without medication prophylaxis. With medication prophylaxis, the risk is about 20-30%
Pregnancy		
Context or Risk factors	**Psychosocial factors**	**Psychiatric conditions**
Pre-existing psychiatric illness, on prophylaxis with accidental exposure to psychotropics	Concerns about teratogenic or other adverse effects Abrupt discontinuation of medications poses risk of relapse Review treatment Screen for major congenital anomalies	High risk of recurrence (60-80%) of severe mental illness (SMI) without medication prophylaxis. With medication prophylaxis, the risk is about 20-30%

	Watch for medical comorbidities	
New onset of psychiatric illness during pregnancy	Hesitation to take medications	Anxiety - 10%-15% Depression - 15-20%
Poor family support, substance use disorder in spouse and domestic violence	Previous female child Marital discord	Anxiety Depression PTSD
Childbirth		
Context or Risk factors	**Psychosocial factors**	**Psychiatric conditions**
Sickness in infant / Separation from infant admitted to NICU / Stillbirth	Worries about health of infant Separation anxiety, guilt Anticipatory grief	Anxiety & PTSD Depression Grief
Stress related to gender of infant	Previous female child Family expectations for male infant Can lead to domestic violence or marital discord	Adjustment disorder, Depression

Table 2: Overview of Postpartum Psychiatric Conditions

Postpartum		
Condition & Prevalence	**Presentation**	**Suggested interventions**
Difficulties in Mother Infant Bonding (5% of healthy mothers; 40-60% of mothers with psychiatric illness)	Mild disorders – delay, absence or loss of bonding Pathological Anger – verbal or physical aggression	Mild disorders – reassurance or encouraging interactions with infant, contact with infant Pathological Anger – ensure safety and rule out mania or psychosis

	Anxiety regarding care of infant – may not trust others with care of infant Rejection – rare	Anxiety regarding care of infant – allay anxiety
Postpartum Blues (40-50%)	Mild, self-limiting and associated with emotional changes that may or may not progress to depression	Reassurance Adequate social support
Postpartum depression (15-20%)	May be insidious in onset in first few months after childbirth In bipolar disorder, abrupt onset of psychotic depression may be noted	In mild cases, it may improve with psychotherapy alone, but may require antidepressant treatment in moderate to severe cases.
Postpartum psychosis (1-2/1000 live births)	Abrupt onset of behavioural disturbances presenting as (i) mania with psychotic symptoms; (ii) psychotic depression; (iii) acute psychosis; or (iv) catatonia	Requires risk assessment for suicidal and infanticidal risk In-patient care may be required
Obsessive Compulsive Disorder	It may pertain to cleaning-contamination or to obsessive urges or impulses to harm the infant (without actual incidences of harm)	Mild cases may be managed with CBT Anti-obsessional medications (SSRI) may be required in severe symptoms

Outline of clinical assessment of perinatal psychiatric conditions

When the psychiatrist is called for the evaluation of the obstetric patient, the psychiatric evaluation may proceed along the following lines (outlined in **Box 1).**

Box 1: Clinical Assessment in Perinatal Psychiatry

History

- History of current illness, ongoing symptoms and functioning,
- History of medical and neurological illnesses - to rule out thyroid disorder, hypertension, diabetes mellitus, seizures/ epilepsy, headache, visual disturbances, fever with altered sensorium, signs of connective tissue disease such as skin lesions or gum bleeds, arthritis,
- Past history of episodes of psychiatric illness
- Treatment history for prior episodes
- Relevant family, developmental and personal history
- Assessment of the premorbid personality,
- Past pregnancies and their outcomes,
- History of traumatic pregnancies and any past obstetric violence especially in severe labour related anxiety or PTSD
- History of child sexual abuse or sexual assault
- Enquiry must be made into certain aspects of pregnancy such as if it is: Planned / unplanned pregnancy, Wanted / unwanted pregnancy; a precious pregnancy and if the woman has specific worries about her own health or the foetus' health.
- Enquiry is made into details about spouse and family members and the available support.
- History of substance use disorders in the woman as well as spouse must be enquired as the latter is a risk factor for domestic violence and psychological morbidity.

Examination

- ***Physical examination*** must be tuned to detect common medical conditions seen in pregnancy

- General examination must look for pallor, jaundice, blood pressure, pedal edema, thyroid enlargement, skin for signs of bleeding
- Systemic examination must evaluate cardio-respiratory system for any cardiac conditions, neurological examination and for arthritis or other signs of connective tissue disorders
- ***Mental Status Examination*** as per routine psychiatric evaluation
- Particular emphasis is placed on attitudes towards pregnancy, motherhood, concerns and worries about pregnancy or infant health
- Any psychopathology (depressive cognitions, delusions or hallucinations) relating to the infant is specifically noted in this setting
- Suicidal risk assessment and risk of harm to infant is also documented
- ***Diagnosis*** is made using standard criteria such as ICD-10 or DSM-5
- ***Psychometric tools*** may be used for the suggested purposes
- For anxiety - Screening: GAD-7(1); Severity: Hamilton Anxiety Rating Scale (HARS)(2)
- For depression - Screening: Whooley's Questions(3), Patient Health Questionnaire (PHQ-9)(4), Edinburgh Postnatal Depression Scale (EPDS)(5), Hamilton Depression Rating Scale (HDRS)(6); Severity: EPDS, HDRS
- For mania - Severity: Young Mania Rating Scale (YMRS)(7)
- For psychotic illnesses and schizophrenia - Positive and Negative Symptoms Scale for Schizophrenia (PANSS)(8), Scale for Assessment of Positive Symptoms (SAPS)(9) & Scale for Assessment of Negative Symptoms (SANS)(10)
- For Severe Mental Illnesses - Brief Psychiatric Rating Scale (BPRS)(11)
- For assessment of maternal behavioural disturbance - NIMHANS Maternal Behaviour Scale (NIMBUS)(12)
- For mother-infant bonding disorders - Postpartum Bonding Questionnaire (PBQ)(13)
- ***Structured Clinical Interview***

- The Stafford Interview(14) is a detailed interview schedule with nine parts. The first four parts form the prepartum section including the psychosocial context of pregnancy and the next five parts forms the postpartum section beginning with labour / childbirth and mother-infant bonding. The interview schedule provides probe questions along with answers with anchor points that help to rate the severity of the clinical findings. One or more sections of the interview schedule can be applied in isolation for specific clinical or research purposes (eg: Mother-Infant Bonding section to assess the mother-infant bonding)

History includes a routine psychiatric history and in addition specific history pertaining to the perinatal context is elicited. This includes history of past pregnancies and their outcomes, including traumatic pregnancies, obstetric complications and perinatal loss. Current pregnancy details including psychosocial context of pregnancy, support from spouse and family as well as history of substance use and domestic violence is collected. Care is taken to ensuring privacy to the woman and family members as they may not be forthcoming with a history of psychological symptoms in a crowded emergency room or in the obstetric ward.

Physical Examination should be conducted to rule out organic aetiology of the psychiatric presentation. Some of the common etiological possibilities such as hypertension, anaemia, jaundice, thyroid disorders, connective tissue disorders, movement disorders, cerebral and cerebrovascular disorders must be ruled out. In addition to clinical examination, certain investigations (Table 3) and referral to other specialist may be advised to the obstetrician.

Mental Status Examination can be done using the routine format used for general psychiatric evaluation. Particular note must be made if the patient has confusion, perplexity or even frank disorientation as these may alert us to a medical / neurological aetiology. Attention is given to the presence of delusions related to the infant or the presence of hallucinations that refer to the infant. These may have a bearing on the risk assessment that is done. Cognitive functions can be assessed as part of the routine mental status examination and followed up with further structured cognitive assessments which can help us assess the possibility of an organic aetiology.

Risk assessment should include an assessment of risk of suicide, infanticidal risk and risk of harm to others. In every case, specific enquiry must be made about suicidal ideas, plans or any

recent attempts of suicide. We may also use structured tools for assessment of suicide risk. This may include the IS PATH WARM? Signs (15) or any other structured tool for assessment of suicidal risk. Mothers with severe mental illness in the postpartum period may have infanticidal ideas and risk for infant harm. The presence of a depressive disorder and suicidality as well as psychotic symptoms related to the infant can lead to risk of harm to the infant (16). Mothers with postpartum mania may handle the infant in a rough manner leading to potential injuries to the infant. They may also be verbally or physically aggressive to the infant during the irritable phase. Table 4 lists some psychopathology specific to the perinatal period and its clinical implications.

Table 3: Suggested laboratory investigations for diagnosis of common medical conditions occurring in perinatal period

Diagnosis	**Investigation**
Infections	Complete Blood Count, Blood Culture, Urine Culture, Wound site discharge Culture
Dyselectrolytemia	Serum Sodium Serum Potassium Blood Calcium & Parathormone (if indicated)
Uremia	Blood Urea Serum Creatinine eGFR
Diabetes mellitus Diabetic Ketoacidosis Hypoglycemia	Blood glucose levels Urine ketones HbA1c

Anemia	Hemogram with MCV, Peripheral blood smear examination Serum Iron Serum Vitamin B12 levels
Thyroid dysfunction Autoimmune thyroiditis	TSH, (T3, T4 if indicated) Anti-thyroid antibodies
Hepatitis Hepatic encephalopathy	Serum Bilirubin, SGOT, SGPT, ALP USG Abdomen Serum Ammonia
Substance Use Disorders	Urine drug screen
Central Nervous System diseases Head injury / Stroke / Hypertensive encephalopathy / Posterior Reversible Encephalopathy (PRES) Syndrome / Cortical Venous Thrombosis Sheehan syndrome / Wernicke encephalopathy / Acute Demyelinating Encephalomyelitis / Multiple Sclerosis, Anti-NMDA receptor encephalitis Meningitis / Encephalitis	CT Brain (with contrast if indicated). CT is avoided during pregnancy MRI Brain Electroencephalogram (EEG) CSF Analysis (Lumbar Puncture)

Table 4: Psychopathology related to the infant and its implications

Psychopathology	**Implications**
Delusion that foetus is already dead	Psychotic depression Acute psychotic states

Or regarding ill health / major defects in the infant Or that infant has died but the facts are hidden from her (in case of NICU admissions)	Often associated with maternal medical conditions also
Delusions that her infant is blessed or divine or special That others may try to steal the infant	Mania Acute psychotic states Can lead to clinging to infant and rough handling with potential for injuring the infant
Denial of pregnancy	Schizophrenia Psychotic depression Following sexual assault Intellectual disability Poor co-operation during childbirth Usually resolves with treatment
Hallucinations	Command hallucinations may lead to harm to infant or being over protective and clinging
Negative symptoms Catatonic symptoms	Emotional neglect Lack of bonding with infant Under-stimulation of infant may ensue
Agitation Anger towards infant or physical abuse Borderline states Complex Trauma	Poor feeding, rough handling of infant Disorders of mother-infant bonding (pathological anger & rejection type) Anxiety related to safety of infant and bonding problems

Psychometric tools are helpful in the objective assessment of the patient's clinical condition and can help monitor the treatment outcomes. While some scales are useful for screening in the antenatal setting, others are useful in rating severity of psychopathology. Finally, some scale are particularly designed for use in the peripartum psychiatry setting as they assess constructs such

as maternal behaviour and mother-infant bonding or have been adapted for the peripartum setting.

Routine screening for depression and anxiety in the antenatal and postnatal period

While universal screening may tend to overestimate the prevalence of psychosocial disorders or even unduly raise the alarm in the case of false positive screen (~35-40%), the Marce International Society position paper recommends that a basic enquiry into current symptoms using the Whooley's questions, Patient Health Questionnaire (PHQ-9) (4) or Edinburgh Postnatal Depression Scale (EPDS) (5) along with enquiry about past and family history of psychiatric disorders may be useful (17). The Whooley's questions (3) are the first two questions of PRIME-MD, namely:

(1) In the past one month, have you felt down, depressed or hopeless?

(2) In the past one month, have you been bothered by little interest or pleasure in things?

The offer for screening must be backed up with adequate resources to provide timely and appropriate services required for the woman (including appropriate referrals to secondary or tertiary care centers). In larger centers with multi-disciplinary teams, this may be possible within the hospital, however, obstetricians working in smaller centers without in-house counselors or mental health professionals may refer the women appropriately.

Psychometric tools for assessment of severity of psychopathology are Young Mania Rating Scale (YMRS)(7) for assessment of mania, Hamilton Depression Rating Scale (HDRS)(6) for assessment of depression, Brief Psychiatric Rating Scale (BPRS)(11) for assessment of psychopathology in acute psychotic states such as postpartum psychosis and Positive And Negative Symptoms Scale for Schizophrenia (PANSS(8)) for patients with schizophrenia.

Edinburgh Postnatal Depression Scale (EPDS)(5) is a 10-item self-rating scale that is useful for screening of antepartum as well as postpartum depression. It can also be used for rating the severity of depression in women clinically diagnosed with depression. In clinical practice it may be applied as a self-rated instrument assisted by the clinician if the woman needs assistance.

Psychometric tools specific for the postpartum setting include the NIMHANS Maternal

Behaviour Scale (NIMBUS) for rating maternal behaviour and the Postpartum Bonding Questionnaire (PBQ) which is helpful in screening for disorders of mother-infant bonding.

The **NIMHANS Maternal Behaviour Scale (NIMBUS)(12)** is a useful bedside tool that can be applied in the postpartum woman. The tool assesses the mother's behaviour on the following domains: (i) care for the infant's needs; (ii) affectionate behaviour towards the infant; (iii) significant incidents towards the infant; (iv) overall assessment of safety; (v) how the mother handles separation from the infant; and (vi) if the mother was separated from the infant and for what reasons. The scores on the first four domains above are totalled to give an overall rating score. This scale is particularly useful in the in-patient setting for postpartum mothers, but may also be used during out-patient follow-up as it relies upon caregiver information in addition to the observation by the clinical team.

Postpartum Bonding Questionnaire (PBQ)(13) is a screening tool that helps to detect disorders of mother-infant bonding. It is a 25-item scale developed and validated by Brockington et al (2006) and there is a validated 19-item Tamil version available (18). The scale has four subscales which include the dimensions of (i) mild disorder of bonding where there is a delay or a lack of ability to perceive bonding, (ii) anxiety related to infant care – which in the Indian setting leads to mothers not able to entrust care of infant with another reliable caregiver such as her own mother, (iii) pathological anger with or without frank abuse, and (iv) rejection of infant where the mother wants to give up the care of infant either temporarily or permanently.

General approach to the patient in perinatal psychiatry:

If the woman consults during the ***pre-conception period***, and the woman is still symptomatic, we may advise the couple to delay pregnancy. They can plan for pregnancy once the clinical condition stabilises.

In case the woman is on medications and is asymptomatic, a trial of discontinuation may be attempted for women who have history of mild illness such as a mild depressive episode in the past. The risk of relapse and need for early review in case of relapse has to be emphasised in such cases. It is beneficial if there is a supportive caregiver at home who can detect early signs of relapse and bring the patient for management in the event of relapse.

In case of SMI, prophylactic medications are preferrable even if the patient is presently asymptomatic. A medication which is relatively safe in pregnancy and lactation may be chosen.

We may need to taper and discontinue medications that are adjunctive in nature and no longer required. This may include benzodiazepines, beta-blockers and anticholinergic agents. Decision to change the medication to another one with greater safety data may not be required in every case unless the risks of continuing the current medication are high for the given patient. However, abrupt discontinuation of medications must be avoided. Folic acid 5 mg per day is prescribed in all women who are planning for pregnancy.

When a woman presents for ***consultation during pregnancy***, we must emphasise that early and regular antenatal check-up and planning childbirth at a hospital with adequate facilities for maternal and neonatal care, including neonatal intensive care is preferable especially if the mother is taking psychotropic medications. All mothers on psychotropic medications are advised to undergo anomaly scans in early trimester (10-12 weeks) as well as at 16-18 weeks when foetal echocardiography can also be done especially for mothers who are on medications that may be associated with a risk of congenital cardiac defects (eg: SSRI, Lithium).

If it is not a planned pregnancy and there were no prior opportunities to modify the medications in the pre-conception period, medications may be modified as outlined above. For new onset of psychiatric disorder during pregnancy, psychotherapy is preferred for mild illness in the first trimester. However, in case of persistent or worsening symptoms and in women with severe course of illness, medication may be initiated.

Since pregnancy can alter the ***pharmacokinetics of medications***, there may be a need for dose adjustments. A slow rate of gastric emptying and increased intestinal transit time can delay absorption of orally administered medications. Increased plasma volume, lower lean muscle to adipose tissue and changes in plasma protein binding leads to greater volume of distribution for lipophilic medications. Medications that undergo hepatic metabolism are cleared faster due to increase in CYP450 enzyme activity and Phase 2 enzyme activity (Uridine diphosphate Glucoronoyl Transferase) and increased steroid hormone levels. Medications that undergo renal clearance undergo greater clearance due to higher glomerular filtration rate (GFR).

These pharmacokinetic changes may require the following precautions (listed in Table 5).

Table 5: Pharmacokinetic considerations in pregnancy

S.No.	Medication	Changes seen	Precautions to be taken
1.	Antidepressants	Levels may fall in late pregnancy (after 20 weeks)	Symptoms monitoring and if possible drug level monitoring
2.	Lithium	Increase in GFR and fluid volume reduces Lithium level throughout pregnancy and immediately returns to pre-pregnancy level soon after delivery	Check Li levels monthly till 34 weeks, weekly thereafter until delivery Consider repeating Lithium blood levels before and 24 h after delivery (if adequate fluid balance during labour was not maintained) Assess Lithium levels frequently in initial few weeks postpartum
3.	Lamotrigine	May decrease around 50% due to increase sex steroids levels, phase 2 metabolic enzyme UGT. Folic acid supplement may reduce effects of LTG	Serum level monitoring from preconception until first month of postpartum

Lactation Advice

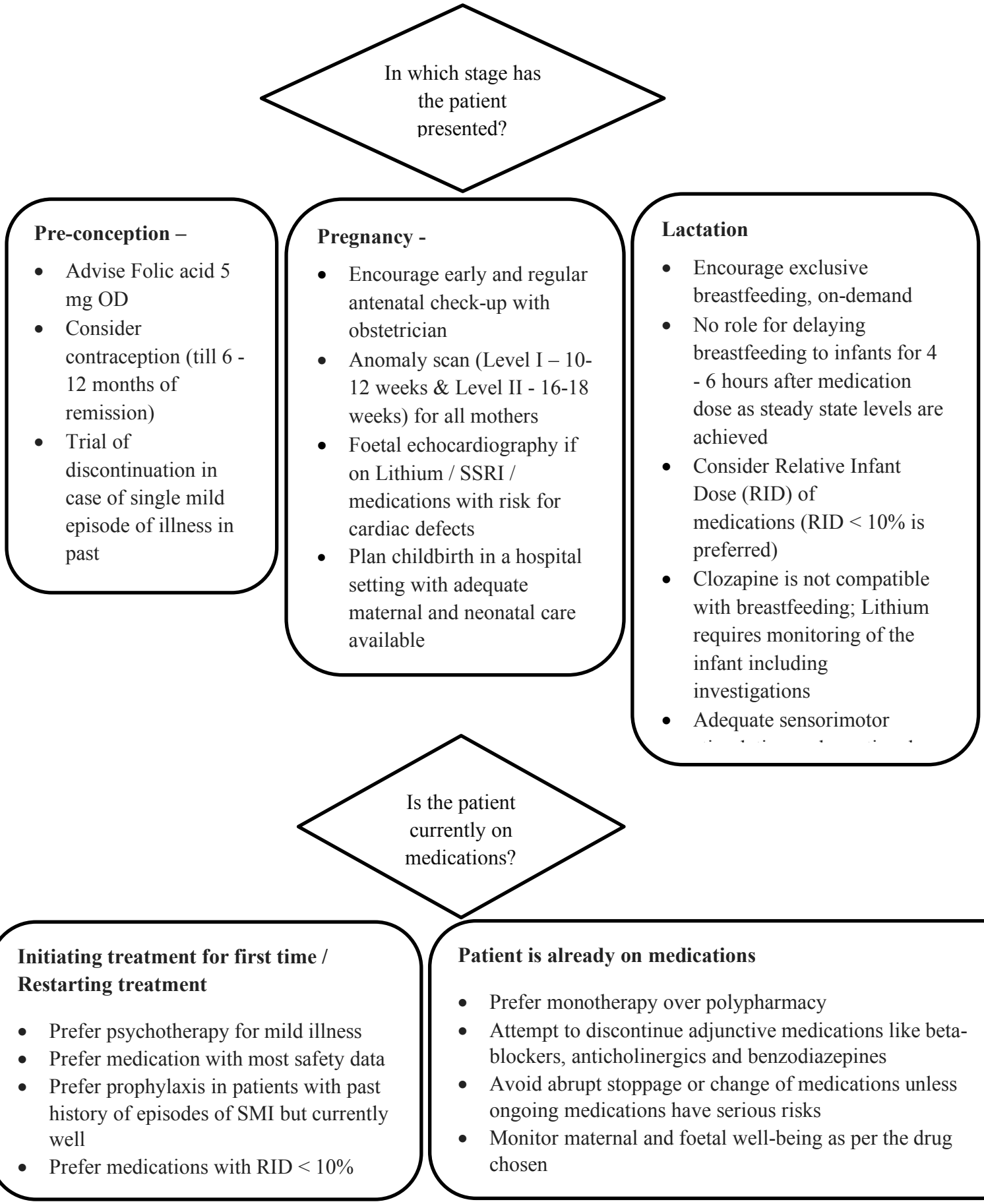
Prefer minimum number of medications, preferably monotherapy in lactation. The medications which have low RID (preferably <10%) are compatible with breastfeeding. Since the medications achieve a steady state level after a few days of treatment, there is no need for withholding breastfeeding for a few hours after each dose of medications. On-demand breastfeeding is recommended. The infant should be monitored for signs of medication related toxicity such as excessive sedation, floppiness, respiratory depression, cyanosis (with sedatives), or excessive crying, irritability, diarrhoea, jitteriness, seizures (with antidepressants) and for rigidity, poor suck reflex, poor feeding, irritability (with antipsychotics). Breastfeeding may have to be withheld in case of any signs of toxicity and a review of medication done. In case of preterm or low birth-weight neonates or neonates with medical or surgical disorders, the advice of the paediatrician or

neonatologist may be sought regarding the safety of breastfeeding. This is important because the metabolism of medications may be affected in neonates with these conditions and they may be at greater risk of adverse effects as compared to healthy neonates who are born at term and have normal weight.

One of the concerns with the use of psychotropic medications has been a possible delay in infant development (19). However, the developmental delay is usually mild and is reversible with the infant catching up with the peers once the exposure to psychotropic medication stops after weaning. Moreover, such delays were more common in low-birth weight or premature infants or those born to elderly mothers (20). In view of this, general advice must be given regarding adequate stimulation of infants. This would include ensuring that the mother or another caregiver is able to provide adequate sensorimotor stimulation to the infant in the form of massage and oil bath, singing lullabies, cooing and talking the infant, providing a variety of colours and sounds through toys, providing an emotional attachment figure to the infant in cases where the mother has severe negative symptoms or sedation due to medications. The possible risks of this mild and reversible delay outweigh the benefits of effective ongoing medications for severe mental illness in the mother.

Figure 1 outlines the general approach to the woman depending on the context of referral. The general advice for the stage at which the woman is seen and general considerations in medical management are listed next.

Figure 1: General approach to management in perinatal psychiatry



Risk Benefit Assessment and Management Planning:

One of the concerns of medication use in perinatal psychiatry is regarding the potential harms of psychotropic medications on the pregnancy and foetal and neonatal outcomes. There is often hesitation among patients, caregivers and other physicians to continue psychotropic medications during pregnancy. Some patients stop medications abruptly once they conceive and risk a relapse of psychiatric illness putting themselves and the foetus at risk.

A risk-benefit assessment with regard to the use of medications in the perinatal period becomes important along with planning of pregnancy in order to mitigate these risks. The four major considerations of risks and benefits to the mother and foetus/ infant that need to be considered are: - (i) risks of untreated maternal psychiatric illness; (ii) benefits of avoiding medication exposure; (iii) benefits of adequate control of maternal illness; and (iv) risks of medications.

The ***risks of untreated maternal depression or SMI*** includes risk of poor adherence to antenatal care, self-neglect and neglect of infant, suicidal risk and/or infanticidal risk, poor nutrition and physical disorders. Risk of domestic violence, substance use and poor obstetric outcomes such as preterm labour, low birth weight and stillbirth increase in patients who are symptomatic.

The risks of untreated maternal illness are weighed against the medication related risks. ***Medication related risks*** include teratogenic potential of medications, potential for maternal morbidity, adverse foetal, neonatal and childhood outcomes. In this section we discuss some of these risks which can aid in decision making regarding psychotropic medications.

The teratogenic risk categories for medications were formerly reported as FDA categories from 1979 to 2015. Some representative medications and their FDA category are listed in Table 6.

Table 6: FDA Categories of medications, safety indication and medication lists

FDA Category	Safety indication	Psychotropic medications in this category
A	Controlled studies have failed to demonstrate a risk to foetus in the first trimester or subsequent trimesters	Folic acid, Thyroxine

B	Animal studies have failed to demonstrate risk of harm to foetus but there are no human studies	Clozapine, Zolpidem, Bupropion, Buspirone
C	Evidence of risk to foetus in animal studies but no well-controlled studies in humans	Most antipsychotics (except clozapine), most antidepressants (except paroxetine), Lamotrigine
D	Evidence of risk of harm to the human foetus however, the drugs may be used in individual patients if the benefits exceed the harm	Lithium, valproate, carbamazepine, paroxetine and most benzodiazepines
X	Significant risk of harm to foetus and the risks exceed benefits	Benzodiazepine drugs such as temazepam, estazolam, flurazepam

These FDA categories were critiqued for being overly simplistic and misleading. They were replaced by the new Pregnancy and Lactation Labelling Rule (21) from 30th June, 2015. The new rules categorise the risks into three headings:

(i) ***Pregnancy related risks*** are mentioned. This includes any information on disease-related risks to mother and foetus or embryo, any dose adjustments required during pregnancy, maternal adverse reactions, foetal / neonatal adverse reactions and finally effects on labour and delivery.

(ii) ***Lactation related labelling*** includes details of presence of drug and active metabolites in human milk, effects of drug on the infant and effects of drug on breastfeeding itself. Information on minimising exposure and monitoring for adverse effects is also listed.

(iii) ***Females and males of reproductive potential***. This section covers the advice regarding requirements for pregnancy testing, contraceptive use before or during drug therapy. It also includes information on the effect of the drug on reproductive potential.

These considerations help us to decide on medication management for psychiatric illnesses in pregnancy and postpartum.

Some key medication related risks are conveyed to the woman and caregivers in terms of risk / potential for major congenital malformations, any increased risk of specific congenital

malformations or adverse maternal and foetal outcomes while comparing these risks with the risk of similar adverse outcomes in women who decide to discontinue medications during pregnancy. Dara from large registry-based studies have suggested that the risks of a particular adverse outcome may not be attributable to the medication itself and may be due to the underlying condition for which the medication is being prescribed. This is called as "confounding by indication".

Table 7 lists the risks associated with some of the psychotropic medications with relative risks which can aid in patient education. However, it is pertinent to note that the evidence in this field is still emerging and it is important to review the latest evidence periodically and adapt the patient counseling accordingly.

Table 7: Summary of risks associated with psychotropic medications (19, 22)

Medications	**Potential complications**	**Pregnancy-recommendations**	**Lactation-Recommendation**
Antidepressants	No increase in Major Congenital Malformations (Most data is for SSRIs) Spontaneous abortion, gestational hypertension and pre-eclampsia, Low APGAR score at birth, low birth weight Third trimester use- neonatal withdrawal syndrome (these risks are minimal, not clinically significant and confounded by underlying depression)	See individual medication class	Considered safe if Relative Infant Dose (RID is less than 10%)
SSRI	Cardiac septal defects with 1st trimester exposure (most with paroxetine)	Sertraline-least placental exposure. Avoid Paroxetine	Sertraline is preferred Fluoxetine may have RID (1.6-14.6%) and

	Persistent Pulmonary Hypertension of Newborn (PPHN) with 3rd trimester exposure (low absolute risk 3 per 1000) Postpartum haemorrhage (SSRI may slight increase the risk) No increased risk of aneuploidy.		may need infant monitoring
TCA	Fetal exposure to TCA is high	Avoid doxepin	Amitryptiline, nortryptiline, desipramine, clomipramine are considered safe
MAO inhibitors	Congenital malformation/Hypertensive crisis	Avoided in pregnancy	Little or no data
Antipsychotics	No increased risk of major congenital malformation	See under each drug class	See under each drug class
SGA Risperidone Aripiprazole Olanzapine Quetiapine Clozapine	Increased maternal weight gain Increased risk of gestational diabetes Increased birth weight Clozapine – risk of floppy infant syndrome	Monitor maternal weight gain Oral Glucose Tolerance Test (OGTT) USG for fetal growth Clozapine – monitor for agranulocytosis	Clozapine is contraindicated
FGA Haloperidol	No major congenital malformation	High potency drugs preferred	Considered relatively safe.

Chlorpromazine Trifluoperazine Fluphenazine	Low birth weight, Preterm delivery Third trimester exposure- Extrapyramidal and withdrawal symptoms		
Mood stabilizers	Used as second-line agents in bipolar disorder (after SGA)		
Lithium	Ebstein anomaly (1/1000)	May be used if benefits exceed the risks	Avoid breastfeeding, OR if breastfed, do foetal blood level monitoring (RID 12-30%)
Valproate	Major anomalies, neural tube defects (6-9%), intellectual disability in child	Avoided	RID (1.5%) Compatible with breastfeeding
Carbamazepine	Increased risk of malformation	Avoided	RID (1-7%) Compatible with breastfeeding
Lamotrigine	No increase in risk of major congenital malformation	Therapeutic drug monitoring needed	RID 9.2 – 18.3% Considered safe with monitoring
Anxiolytics Benzodiazepines	May induce perinatal toxicity, low APGAR score, hypotonia, poor feeding, clef defect, Just before delivery- floppy infant syndrome	Consider tapering BDZ Intermittent use less likely to cause any withdrawal Short acting drugs preferred-Lorazepam	May cause sedation Short acting agents preferred if required – Lorazepam (RID 2.5-3%)

Process of discussion of risks and benefits of medications with mothers and their families

Once the clinical assessment is completed and a decision is made that the woman will have more benefits than risks of taking medications, the following discussion is suggested with the woman and family regarding the medication options (Box 2).

Box 2: Discussion of medication risks and benefits

When:

- All women of childbearing age who are receiving psychotropic medications must be sensitized about risks and benefits of psychotropic medications
- Pre-conception counselling may be initiated at the first visit when the woman plans to get married or presents after marriage
- Most women present for consultation during pregnancy after psychotropic exposure has already occurred as the majority of pregnancies are unplanned or women have less control over contraception. Hence it is important to involve the woman and her partner in discussions regarding contraception and spacing of pregnancies.
- Women of child bearing age with a past or family history of mental illness or on psychotherapy may also be educated about it in case of future requirement

Whom:

- Counselling should include the woman and the primary caregivers especially the spouse, if available
- Only if the woman does not have the capacity to decide, nominated representative / caregiver should be involved primarily in the discussion

Why:

- Most pregnancies are unplanned and psychotropics exposure to the foetus can be avoided
- On unintended exposure, the woman and caregivers may stop medications abruptly leading to high risk of relapse in the case of SMIs

How:

- The possible medication options (individualised for the woman) may be listed out
- The benefits of medication prophylaxis can be discussed. This includes relapse rates in women who receive prophylaxis as against those who discontinue prophylaxis for the given condition

- The risks of relapse or untreated maternal mental illness on the outcomes of pregnancy and foetal-infant health can be discussed
- This is followed by a discussion of potential risks and benefits of psychotropic medications

What:

- The specific details of risk where available can be given
- Use of visual aids or charts can help
- Information about embryonic / foetal development in each trimester of pregnancy and specific risks associated
- The risks may be presented in terms of relative risk (i.e. the use of drug X increases the risk of cardiac defects to 1.4 times compared to that foetuses not exposed to drug X)
- Absolute risks may be presented with a common denominator for ease of grasping –example given in **Figure 2**

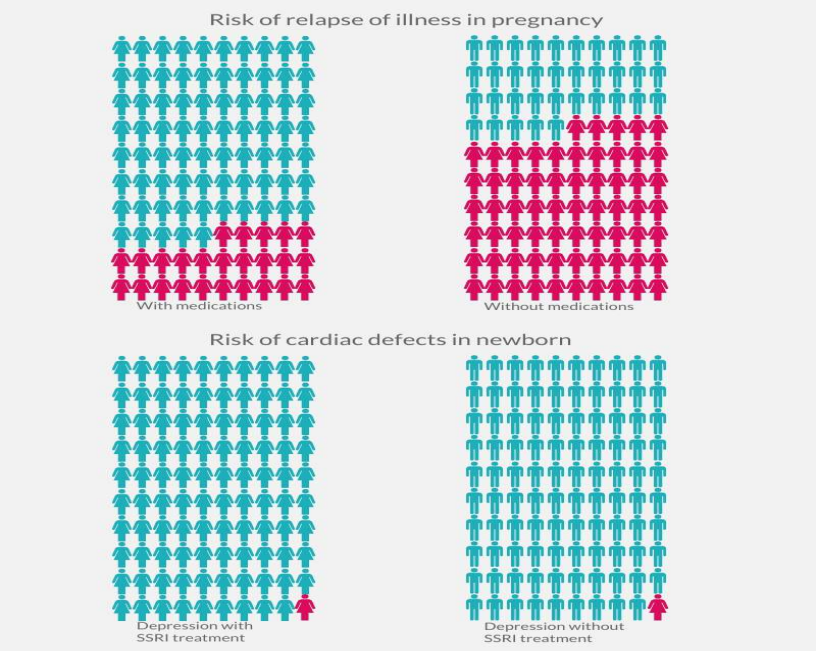
Exposure:

- In case of exposure to psychotropics in first trimester, decision to continue or change the medication and assessments for foetal anomalies must be done

Documentation

- Brief documentation of the discussions held with the woman and caregivers, their concerns raised and clarifications given and their decision (if there are multiple options offered) may be documented

Figure 2: Sample risk graphics to show risks during pregnancy



Management of Psychiatric Disorders in the perinatal period:

Common mental disorders include anxiety, depression and related disorders such as adjustment disorder are usually amenable to psychotherapy in the initial stages and when they are mild in severity. Therefore, the principle is to treat mild episodes of these disorders with psychotherapy alone. Cognitive Behaviour Therapy (CBT) may help in anxiety as well as depression. Interpersonal Psychotherapy (IPT) may help in depression and Exposure and Response Prevention (ERP) may be provided for treatment of OCD. If the anxiety or depressive symptoms are persistent, recurrent or are worsening in severity; or if there is poor response to psychotherapy alone - medication may be prescribed for management of the illness.

Anxiety disorders: Some women experience anxiety or stress related to infertility and treatment for infertility, previous pregnancy loss, fear of pain during labour (tokophobia) and concerns about traumatic experiences during pregnancy. In such cases, management involves psychoeducation, supportive counselling and reassurance by obstetrician after due antenatal check-up. In case these measures do not help, more structured psychotherapy or medications may be considered as in the case of anxiety or depression.

Selective Serotonin Reuptake Inhibitors (SSRI) (except paroxetine) are the medication of choice for the management of anxiety disorders in pregnancy. Buspirone (FDA category B) does not have many human studies to support the use.

Depressive disorders: In the case of depressive disorders, the risk-benefit assessment for considering medication prophylaxis has the following considerations. Women who have had a single mild episode of depression in the past, may be given a trial of discontinuation of antidepressant medications if they are asymptomatic for 6-12 months. However, those who have had more severe illness such as recurrent (four or more lifetime episodes) of depression, or have had severe depression with psychotic symptoms, or had suicide attempts during the depressive episode or have required hospitalisation or electroconvulsive therapy for control of depressive symptoms in the past will benefit from continuing the antidepressant prophylaxis (23). The presence of domestic violence and previous traumatic experiences increase the risk and presence of adequate social support is a protective factor against depression.

Obsessive Compulsive Disorder: For mild severity of symptoms, previous response to ERP/CBT with prolonged remission and absence of significant comorbidity like depression may allow a trial of discontinuation of SSRI treatment. However, in more severely ill women with comorbid depression or suicidal risk, the risks of discontinuation of medication may exceed the benefits.

Management of Severe Mental Illness in perinatal period:

Severe mental illness (SMI) refers to Bipolar affective disorder and schizophrenia. In the context of perinatal psychiatry, severe behavioural disturbances can also occur in postpartum psychosis as well as postpartum depression which is often of abrupt onset, with severe symptoms, psychotic symptoms and suicidal risk.

The risk of relapse of bipolar disorder is as high as 66% in women who discontinue prophylaxis as opposed to about 25% among those who continue prophylaxis (24). Women with schizophrenia are also advised to continue prophylaxis in the perinatal period. Second generation antipsychotics (SGA) are preferred for prophylaxis. There is a risk of increased weight gain as well as gestational diabetes (GDM) with SGA and women should be monitored for excessive weight gain and asked to undergo Glucose Tolerance Test (GTT) during pregnancy (19).

Bipolar disorder: Monotherapy with SGA is preferred as outlined above. In bipolar depression, there may be a need to add antidepressants for a short period of time in some women. Some women may require the addition of a mood stabiliser.

Valproate and carbamazepine are avoided during pregnancy due to the risks of congenital malformations and neurodevelopmental disorders (25). However, low-dose lamotrigine (< 325

mg per day) may not be associated with risk of major congenital malformations and may be continued in women with bipolar depression after discussing the risks and benefits (26). Similarly, in women who have required lithium prophylaxis to remain well, it may be considered after discussion with the woman and caregivers. Therefore, when SGA alone is not effective as prophylaxis and a mood stabiliser is required, lithium or lamotrigine may be considered as per the woman's clinical profile.
Relapse prevention strategies for bipolar disorder include: avoiding sleep deprivation, stress management, ensuring medication adherence, avoiding substance use and knowledge of early warning signs of a recurrence with self-monitoring of symptoms.

Schizophrenia: Monotherapy with antipsychotic medication is preferred for the management of schizophrenia. SGAs are usually preferred when treatment has to be initiated. While first generation antipsychotics (FGAs) or long-acting antipsychotics (LAIs) are not initiated for treatment of schizophrenia during pregnancy. This is because there is less safety data regarding these medications. In case a woman is maintaining well on FGAs and a change of medications carries the risk of relapse, we may decide to continue the medications after discussion with the woman and family. In case a woman conceives while of effective treatment with Long-Acting Injectable (LAI) antipsychotics, the discontinuation may not immediately reverse the possibility of adverse effects as the clearance of these LAI drugs may take weeks after stopping treatment (27). While most antipsychotics are compatible with breastfeeding and have RID<10%, clozapine is contraindicated in breastfeeding.

For the management of severe postpartum psychiatric conditions, medications compatible with lactation are preferred. Postpartum Depression (PPD) typically begins within the first 4 weeks following delivery, but the risk period can be up to 2 years post-delivery. In mild cases, it may be managed with antidepressants alone. In cases of psychotic depression, an antipsychotic is also prescribed. However, bipolar disorder must be ruled out in women before prescribing antidepressants for long periods of time. Severe illness, where suicidal risk is high, may warrant in-patient care to ensure safety of patient, infant and others family members. Women with a previous episode of PPD, may be given prophylactic antidepressants in the postpartum period. Brexanolone, (allopregnanolone) is an endogenous progesterone metabolite which acts as an allosteric modulator of the GABA-A receptor. Brexanolone is recommended for moderate to

severe PPD in a stepped dosing pattern as follows: 30 µg/kg/hour in first 4 hours, followed by 60 µg/kg/hour for next 20 hours, then at a maximal dose of 90 µg/kg/hour for next 28 hours and then stepped down to 60 µg/kg/hour for 4 hours and 30 µg/kg/hour in the last 4 hours. The administration of the requires close monitoring in an in-patient setting. Headache, dizziness, fainting or syncope are the major adverse effects reported. The drug though approved by FDA is yet to be launched in India.

Postpartum psychosis (PPP) is a severe mental illness which has abrupt onset in the postpartum period (usually within 4 to 6 weeks of childbirth). It may present as any one of the following clinical syndromes – acute mania, acute and transient psychotic disorder, catatonia or as psychotic depression. The specific underlying disorder must be treated after ruling out medical conditions that can mimic postpartum psychosis. In addition, PPP is also often severe in presentation with suicidal risk or risk of harm to the infant or others. This may often require in-patient care for adequate management of symptoms. The mainstay of management of PPP is usually a SGA which is compatible with breastfeeding. While SGA alone may suffice in case of acute psychotic presentations, psychotic depression may require addition of an antidepressant. In case of mania, a mood stabiliser may be initiated. Catatonia is common in pregnancy and postpartum period. About 20% of women admitted in the perinatal period had catatonia as opposed to about 8% of admissions to acute in-patient psychiatric units (28). The management of catatonia in pregnancy often presents with a particular difficulty in management because it necessitates the use of a benzodiazepine – lorazepam for its management. However, the symptoms of withdrawal and refusal to eat can cause dehydration, hypoglycaemia and electrolyte imbalance. The presence of stupor or immobility increases the risk of venous stasis and deep vein thrombosis during pregnancy. Therefore, the benefits of treatment with lorazepam often exceeds the risks associated with its use for patients having reduced oral intake, rigidity and immobility.

Typically, management can be initiated with low-dose of lorazepam 3 to 8 mg per day (given in divided doses of 1-2 mg three or four times a day). In case of inadequate response over the first 24-48 hours, the dose may be increased to 8 to 16 mg per day while monitoring for maternal pulse and blood pressure and foetal heart rate. Further doses may be withheld if maternal pulse is below 60 bpm or blood pressure is below 90/60 mmHg or foetal heart rate is below 100 bpm. When

lorazepam is used, attempt must be made to reduce the dose and discontinue the medication while monitoring for symptoms of relapse. Another psychotropic medication must be initiated according to the underlying diagnosis. Electroconvulsive therapy is the other option for the management of catatonia that does not respond to lorazepam alone.

Table 8 summarises the management strategies for various psychiatric disorders depending on the clinical aspects of the disorder in a given patient.

Table 8: Overview of preferred line of management for psychiatric disorders in perinatal period

Disorder	**Clinical aspects**	**First-Line or Primary treatment**	**Second-Line or Secondary treatment**
Adjustment disorder OR Mild Anxiety		Psychoeducation Psychotherapy (CBT / IPT) Follow-up and monitoring for symptoms	Medication may be considered for women with persistent symptoms, severe episode in the past or strong family history
Depressive disorder	Mild / single episode of depression - mild & in the past	Psychoeducation Psychotherapy (CBT / IPT) Follow-up and monitoring for symptoms	Medication may be considered for women with persistent symptoms, severe episode in the past or strong family history Note- Always rule out any history of bipolarity such as milder highs, hypomanic episodes or a strong family history of bipolarity before starting an antidepressant
	Mild depression - active	Psychotherapy	Antidepressants if persistent symptoms or

			severe past episodes or strong family history
	Moderate to Severe Depression	Antidepressant medications (SSRI)	Psychotherapy (in combination with medication)
	Recurrent depressive episodes (>= 4 episodes) OR Recently remitted moderate to severe depression	Antidepressant prophylaxis	Psychotherapy and relapse prevention measures such as enhancing coping skills, stress management
Obsessive Compulsive Disorder	Mild, amenable to ERP / CBT and prolonged remission	Continuing ERP / CBT booster sessions and medication free follow-up	SSRI as antiobsessional medication may be used
	Severe or persistent with comorbid depression	SSRI may be considered for treatment and prophylaxis, if on clomipramine, the same may be continued while monitoring for any adverse effects	Add-on ERP / CBT may be considered
Bipolar disorder	Mania	Monotherapy with Second Generation Antipsychotic (SGA)	Mood stabiliser (Lithium) - added if no response to SGA alone or on effective ongoing treatment with

			Lithium after discussing with the mother and family
	Depression	Monotherapy with SGA (olanzapine / other SGA) Use antidepressants with great caution because of a chance of postpartum relapse. If depression is severe and does not respond to SGAs then consider a Combination of SSRI + SGA (eg: fluoxetine + olanzapine)	Mood stabiliser (Lithium) - added if no response to SGA alone or on effective ongoing treatment with Lithium
	Remission	Monotherapy with SGA	Mood stabiliser (Lithium) - added if no response to SGA alone or on effective ongoing treatment with Lithium
Schizophrenia	Exacerbation or episode	Monotherapy with SGA	Short term benzodiazepines may be required with non-sedating SGAs
	Remission or negative symptoms	Low dose SGA	Psychosocial interventions
Catatonia	PPP, mania or depression	Lorazepam may be preferred	Electroconvulsive Therapy,

			Treatment of underlying illness – mania or depression with either SGA / mood stabiliser / antidepressants as per clinical presentation

Management of Alcohol Use Disorder during pregnancy

Foetal exposure to alcohol is associated with growth restriction, facial anomalies and central nervous system dysfunction such as low intelligence and inattention-hyperactivity in the child. No level of alcohol use can be considered as safe in pregnancy. Women must be educated about the risks of alcohol use and advised against drinking. Low levels of alcohol consumption may require brief intervention or motivational interviewing, however, those with moderate or high-risk use may require specialist deaddiction intervention.

Mothers with alcohol dependence who experience significant withdrawal symptoms can be treated with a short-course of benzodiazepine medications. Lorazepam or diazepam may be considered for detoxification in case of severe withdrawal symptoms.

Long term prophylaxis for relapse prevention relies upon motivational interviewing and relapse prevention strategies. There is not much safety data to support the routine use of medications such as naltrexone or acamprosate. They may be prescribed in women who have high risk of relapse. Disulfiram is avoided in pregnancy.

Management of other substance use disorders in pregnancy and postpartum

Cannabis use is associated with an increased risk of mood disorders, autism spectrum disorders and inattention-hyperactivity in the offspring.

Tobacco use is associated with risk of preterm birth, low birth weight and malformations of lips and mouth as well as risk of increased maternal bleeding during labour.

Psychotherapeutic methods are preferred for low levels of use. There is not much evidence for the safety of Nicotine Replacement Therapy (NRT) including patches and bupropion (FDA Category B) for treatment of tobacco use disorders. Limited evidence suggests that they may not increase the risk of adverse neonatal outcomes (29). The evidence for safety of these medications is not extensive and hence treatment decisions must be taken on an individual basis.

Suicide in pregnancy and postpartum

The risk of suicide among women is higher in the first year after childbirth than any other time in their lives. Younger age, belonging to a middle socioeconomic status, poor perceived support, domestic violence, depressive symptoms, and having a past history of suicidality predict suicidal risk. Women are also more likely to use more lethal methods in perinatal period. Suicidal risk and infanticidal risk may occur together and require attention. In-patient care may be considered along with ensuring the presence of family members and adequate social support to ensure a careful watch over the mother during the period of suicidal risk is essential.

Box 3 summarises interventions specific and appropriate for women with suicidal risk in the perinatal period

- Hospitalisation is needed in a High Intensity Care unit and temporary separation from the infant in a postpartum mother till risk for suicide decreases
- Ensure continuation of breast feeding as much as possible through expressed breast milk or infant visits to the mother and restitution of joint admission once suicidal risk decreases
- Use ECTs to enhance recovery if suicidality is in the context of depression or psychotic symptoms
- Educate family members about the high risk for self-harm and eyeball to eyeball monitoring till risk is found to decrease
- Twice daily risk assessments for lethality and intentionality
- Ensure that the ward or home is safe and no sharps are available

- Women at risk for suicide may want to take their infants and leave home or the hospital and utmost care needs to be taken to ensure safety
- **Note**- In High Income countries one of the foremost reasons for maternal mortality is maternal suicide often due to a severe mental disorder

Management of Agitation in the Perinatal Psychiatry setting

Agitation in the peripartum setting can put the mother and foetus / infant to risk of harm. Verbal de-escalation must be done first followed by oral medication such as lorazepam 1-2 mg or promethazine 25-50 mg or olanzapine 5 – 10 mg or chlorpromazine 50 – 100 mg. In case oral medications are not effective, intramuscular injection of lorazepam 2 mg or promethazine 25 – 50 mg or haloperidol 2.5 – 5 mg (in combination with promethazine to prevent dystonia) or olanzapine 10 mg may be considered. Regular monitoring of temperature, pulse rate, respiratory rate, blood pressure and foetal well-being measures may be essential. Care should be taken to ensure that patient is lying supine with right hip elevation to avoid compromise of blood supply to foetus.

Electroconvulsive therapy (ECT)

The use of electroconvulsive therapy (ECT) during pregnancy may be life-saving in certain cases. Patients with catatonia or severe suicidal risk secondary to depression who do not respond to medical management alone may be considered for ECT. Some additional precautions taken during ECT in pregnancy are outlined in Box 4.

Box 4: Use of electroconvulsive therapy in pregnancy

Prior to procedure

- Obstetric consultation and clearance in addition to pre-anaesthetic check
- Overnight fast of 8 hours may suffice
- Avoiding anticholinergic medications (as they reduce lower oesophageal sphincter tone) and use of oral antacids 15-20 mins prior to procedure may reduce risk of gastric reflux
- Ensure adequate hydration with normal saline or ringer lactate

During procedure

- Pre-oxygenation is essential, but avoid hyperventilation to ensure adequate foetal oxygenation
- Anticholinergics - glycopyrrolate is preferred as it does not cross placenta
- Right hip is elevated (after 20 weeks gestation) to avoid aorto-caval compression leading to foetal blood flow compromise
- Monitor foetal heart rate by Doppler just before and after ECT is administered. Twice weekly non-stress test (NST) may be repeated
- Seizures do not lead to uterine contractions directly, but due to oxytocin release, painful contractions may occur. If persistent, tocolytics may be given

General

- ECT during pregnancy must be given in a setting where emergency obstetric and neonatal care is available readily
- In the postpartum period if ECTs are being given, ensure that the infant is fed before the procedure, the postpartum mother is prioritised in the ECT chart to receive the ECT early and expressed breast milk is available for infants

Repetitive transcranial magnetic stimulation (rTMS)

The safety of rTMS during pregnancy has not been widely studied, however, the few studies that have been done in pregnancy have not reported any adverse maternal or infant related outcomes due to rTMS (30).

Mother Infant Bonding Interventions in women with psychiatric problems

Many mother infant dyads will have been separated from each other or may have difficulties in forming attachment because of a mental health problem in the mother. Early attachment problems are a risk for later externalising and internalising problems in the child and other emotional difficulties in adolescence and adulthood. Adequate attention should be paid to assessment of bonding using the instruments mentioned above and a good clinical interview. If a bonding problem is found interventions include- education about the same training in infant care,

modelling, video enabled feedback training and in case of a severe problem, mother-infant psychotherapy. Having an additional caregiver such as a grandmother or father is often beneficial.

In-patient care of perinatal mothers and the Mental Healthcare Act 2017:

The Mental Healthcare Act, 2017 recommends the least restrictive option for patient care. Therefore, out-patient care is preferred in mild psychiatric illnesses or exacerbations. However, in moderately severe illness episodes or exacerbations, in-patient care may be required to ensure safety of mother and infant. When in-patient care is provided to a mother with low risk of suicidal or infanticidal risk, rooming-in of mother and child (under three years of age) is recommended as per Section 21(2) of the Mental Healthcare Act, 2017. In case a decision to separate the mother and baby is made by the treating psychiatrist based on information available regarding the patient's illness and an assessment of the patient's clinical condition; the decision must be reviewed every 15 days. In case the separation must continue beyond a period of 30 days, the Mental Health Review Board must be informed and permission sought for the same.

Mother and Baby Units (MBU) are in-patient units with at least four in-patient beds which allow the rooming-in of mothers and their infants or children under the age of three years and are run by a multi-disciplinary team of psychiatrists and allied health professionals. The requirements of setting up an MBU in India have been outlined by Chandra PS et al, 2015 (31). There may be a need to set-up MBUs in the future.

Conclusion

The role of a psychiatrist in the care of mothers with mental illness broadly includes evaluation and management of mothers with: (i) psychological issues related to all aspects of pregnancy and childbirth such as infertility and its treatment, traumatic experiences related to pregnancy and childbirth; (ii) management of new onset psychiatric conditions in the perinatal period; and (iii) management of pre-existing psychiatric illnesses in mothers planning pregnancy.

The major decisions regarding choice of treatment is taken based on risk-benefit analysis of treatment of the psychiatric condition against the risks of untreated psychiatric illness in the mother. In general, the benefits of prophylaxis for mothers with SMI exceeds the risks. Individualised decision may need to be taken in each case. The new legislation, Mental Healthcare Act 2017, encourages the setting up of specialised Mother and Baby Units (MBU) for the joint admission of mothers with their infant or children under the age of three years.

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Psychiatric assessment of persons for solid organ transplant

Psychiatric assessment of persons for solid organ transplant

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Abstract

Advancements in the field of solid organ transplantation have resulted in improved outcomes for the recipients. This has resulted in increasing numbers of transplant procedures being carried out worldwide. Psychiatrists are called to assess both before the transplantation (for potential donors and recipients) and after the transplantation. The assessment is geared according to the reasons of evaluation. The psychiatrist can play an important role in conjunction with the transplant team in improving the outcomes of the patient. The present guidelines discuss the salient features of psychiatric assessment of persons who are about to undergo the transplantation procedure and those who have already undergone the surgical intervention. The salient features of the steps of the assessment are presented, and the various psychiatric and psychosocial issues of relevance are elaborated upon. The legal framework of transplant in India and the ethical considerations are also presented in the text.

Introduction

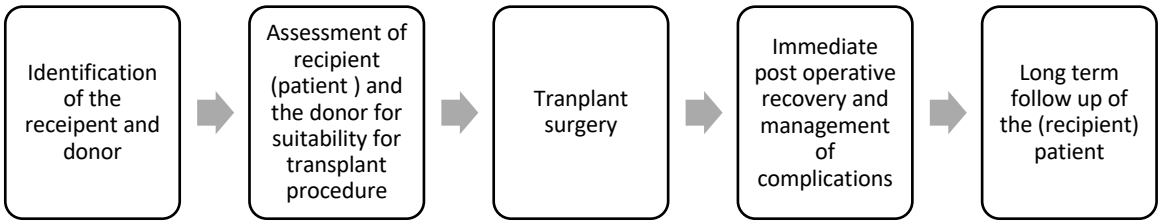
Organ transplantation, a lifesaving procedure, has emerged as a ray of hope for individuals with acute or chronic organ failures.[1,2]Gradual advancements in the field of transplant medicine haveincreasedthe rates of transplantation worldwide and have incrementally improved the outcomes of the patients undergoing such transplant procedures. The first successful solid organ transplant was conducted by Dr. Joseph Murray, who performed a kidney transplant on a patient with acute renal failure, with an organ donated by his identical twin brother. The use of immunosuppression to reduce the rates of rejection hasled to a higher longevity of patients after transplantation. Refinement of patient selection, expertise, and training in transplant surgeries, dedicated teams for the conduct of transplantation and follow-up of patients, advancements of immunosuppressant protocols have all resulted in better outcomes for patients, leading to many patients surviving decades after transplant. In India as well, there is a gradual rise in the number of patients undergoing organ transplantations.[3]

Organ transplantation can be classified in many ways.[4] Organ transplanted in the same individual is known as an autograft, while the transplantation of an organ from another individual is called an allograft. Allografts can be from a living donor or a deceased (cadaveric) donor. Solid-organ transplants typically include transplantation of kidneys, liver, heart, intestines, lungs, and pancreas. Among these transplants, kidney transplant is the most common solid organ transplant conducted worldwide. Corneal transplants, skin transplants,

and stem cell transplants are generally not included under solid organ transplants. Transplantation can be carried out in a planned elective manner (in cases of chronic organ failure, for example, renal failure consequent to diabetic nephropathy), or on an emergency basis (in cases of acute organ failure, for example, liver failure after taking high doses of acetaminophen).The conduct of the transplant is contingent upon the availability of the organs. While the wait may be minimal for a live donor transplant (which can be done for kidney and liver transplants), the waiting times can be considerable for cadaveric transplants (like heart transplants). Many countries have registries that maintain a list of patients who require a transplant and are allocated the organs when organ donation occurs after the death of individuals who had pledged to give away their organs or when the family members agree for organ donation.

Organ transplantation is generally carried out in specialized centers with expertise in conducting such procedures. The team comprises surgeons, anesthetists, internists and critical care specialists, and mental health professionals, trained nurses, perfusionists, dieticians, and other professionals involved in the care of the patients. The team approach helps in the proper assessment, conduct of transplantation and after-care of patients. Solid-organ transplantation is a highly skilled surgical procedure, and dedicated centers help to develop expertise and refine skills for the conduct of transplantations. Opportunities for specializations have been developed in this field, and trainingis offered to professionals who want to enhance their knowledge and skills in this area. A generic schematic of the solid organ transplant workflow is presented in figure 1.

Figure 1: Schematic representation of solid organ transplantation process



Mental health professionals should be included in transplantation teams as varied mental health issues are faced by the recipients and donors. The skills of the mental health professionals complement those of the surgeons and other specialists of the team in dealing with the patient and improving the outcomes by recognizing various psychosocial issues, identifying diagnosable psychiatric disorders, , highlighting and managing specific behavioral issues, and flagging pertinent ethical concerns.[5–9] Involvement and importance of the mental health professionals in the transplant teams can be understood from the perspective that, this has given rise to a subspecialty of transplant psychiatry. Thus, psychiatrists should be made a part of the hospital team that assesses the suitability of the candidates (both recipients and donors) for transplantation.

The present guidelines cover the mental health assessment of persons undergoing solid organ transplants. These guidelines focus on the pre-transplant assessments, assessments in the immediate peri-transplant period, assessments after the transplantation and during follow-up. These guidelines also focus onthe assessment of the donor and specific issues related to the donor, and the relevant psychosocial issues. The relevant legal framework in India pertaining to solid organ transplantsis also discussed. These guidelines provide broad framework for the assessments pertaining to the solid organ transplants. However, these guidelines are not a substitute for the professional knowledge. The assessment procedures and management

mentioned in the guidelines may be relevant to the ideal situation, where the adequate manpower is available for carrying out such assessments. Across India, there is wide variation in the availability and involvement of the mental health professionals as part of the transplant teams. Hence, following these guidelines will be guided by the feasibility issues and the available manpower.

Role of Psychiatric Assessments

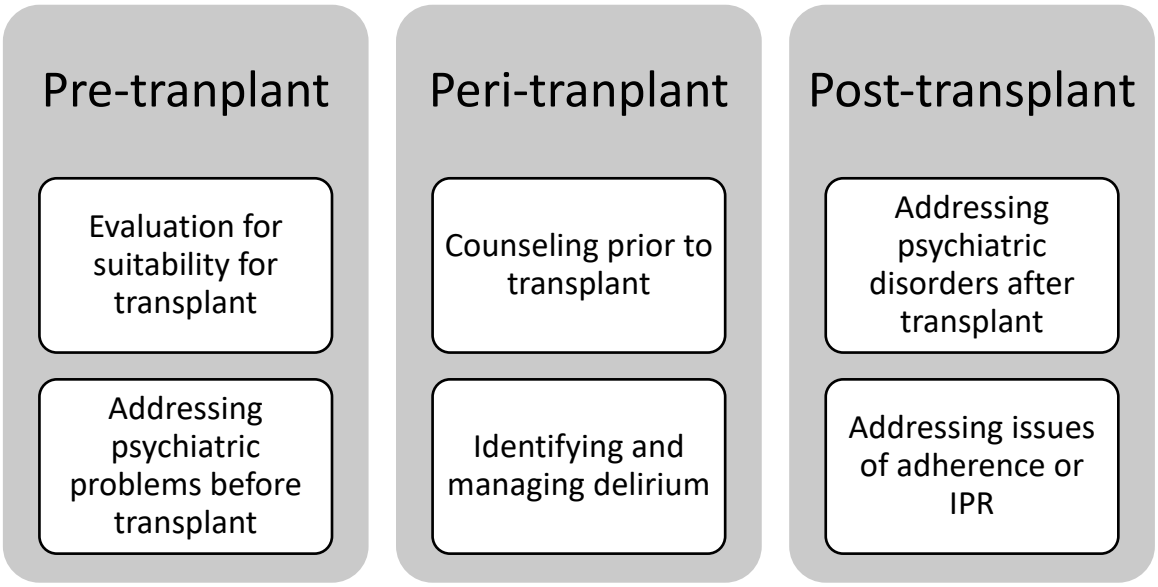
Psychiatrists have an important role in evaluating patient suitability for solid organ transplantation

Table 1: Reasons of psychiatric assessments for patients undergoing solid organ transplantation

Pre-transplant evaluation of the recipient
Pre-transplant evaluation of the donor
Managing psychological issues and psychiatric condition before the transplantation
Managing apprehension of the patient before transplant surgery
Managing post-transplant delirium
Addressing psychological issues and psychiatric disorders if they emerge after the transplant
Managing issues of adherence to medications, dietary restrictions and other recommended behavioral changes
Providing guidance on ethical issues
Interpersonal issues between the patient/family and the member(s) of the treating team

There can be various phases related to transplantation while inputs from the psychiatrists are called for (Table-1 and Figure-2). The setting of evaluation, the profile of problems anticipated and encountered, and theexpected interventions or suggestions vary. While pre-transplant evaluation can be conducted in an office-based practice setting, evaluation of delirium or acute confusional state may need to be conducted in intensive care. A report mentioning suitability of the patient for undergoing transplantation may suffice for a planned transplantation procedure, with the patient evaluated on a single occasion. For a patient who manifests with delirium, the psychiatrist may need to closely align with the transplant team and initiate medications, as well as non-pharmacological interventions like reorientation cues, while the other members of the team attempt to identify and correct underlying causes like infection, anemia, or medication side effects. The psychiatrists can play an important part in the transplant team by facilitating effective communication with the patient and resolving ethical conundrums as well.

Figure 2: Inputs from psychiatrists during various phases of the solid organ transplant



IPR- Interpersonal Relationship

Pre-transplant psychiatric assessment of the recipient

Assessment of the recipient is geared towards evaluating for the presence of pre-existing psychiatric illnesses or vulnerabilities that are likely to significantly hamper the outcomes of the patients. It also aims to assess whether the patient is competent to comprehend the magnanimity of the decision to undergo the transplant and to confirm whether the patient is aware about the intricacies of undergoing the procedure and is willing to go through the process of transplantation. Such an evaluation is done during the preparatory phase when an individual is awaiting an organ transplant.

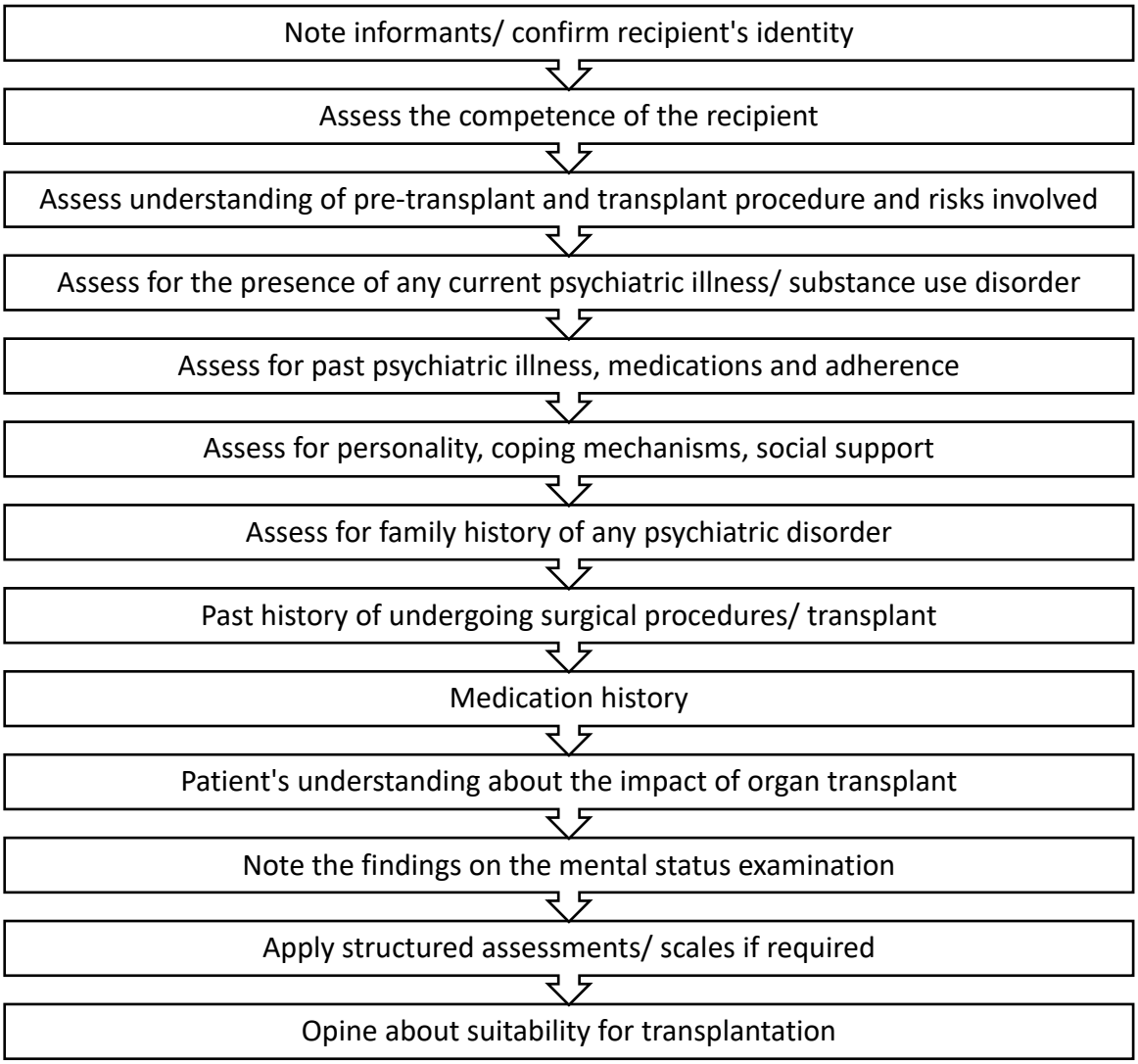
The issues to consider during the pre-transplant assessment of the recipient are shown in table 2 and figure 3. It may be remarked that evaluation may need to be conducted on more than one occasionifspecific issues are to be clarified. Such an assessment can be carried out at the outpatient setting or the bedside if the patient is admitted. Information from multiple informants would help to get a clearer picture.

Table 2: Pre-transplant assessment of the recipient

Note who all provided the information
Confirm the identity of the recipient
Assess the competence of the recipient
Assess the understanding of the patient of the pre-transplant and the transplant procedure and the risks involved
Assess for the presence of any current psychiatric illness,
Assess for the presence of any substance use disorder including the last intake, past history of efforts to abstain, lapses and relapses, etc.
Assess for the presence of any psychiatric illness in the past: severity of symptoms, course of the symptoms, response to treatment, side effects of medications, adherence to medications, time to relapse in case the psychotropics are stopped
Assess for personality and coping mechanisms

Assess for family history of any psychiatric disorder
Past history of undergoing surgical procedures: reaction of the patient to the hospitalization, adherence to the suggested recommendations, reaction to prolonged hospital stay, including the intensive care unit stay
Past history of transplant: in case the patient has undergone transplant in the past- reason for organ failure, time to failure, psychological reaction of the patient and the family to the failure
Medication history: any psychiatric issues while receiving various medications (for example, past history of steroid associated psychiatric manifestations)
Social support
Patient's understanding about the impact of organ transplant: restrictions in the movements, dietary restrictions, regular medication intake, abstinence from the substance(s), following measures to prevent infection, etc.
Note the findings on the mental status examination including the level of cognitive functioning
Apply structured assessments/ scales if required
Opine about suitability for transplantation

Figure 3: Pre-transplant evaluation of the recipient



The assessment interview generally begins with developing rapport with the identified recipient and engaging in a conversation about the medical illness which has necessitated the transplant. The psychiatrist can ascertain competence of the recipient during the process of the initial interview. It is helpful to know whether the patient understands what is going to happen prior to the transplant and during the transplantation, what kind of risks are anticipated, and what precautions or regimens would be required after the transplantation surgery is conducted. If the patient is unclear about the surgical procedure or the commitments required from his/her perspective, then the patient may be referred to the surgeon for clarification. If the patient is found to be not competent, then the legally accepted representative should be able to consent to the procedure (the same is applicable for minors). However, a challenge in such situations is to determine whether the legally acceptable representative or nominated representative truly represents the best interest of the patient and will continue to be responsible for the wellbeing of the transplant recipient after the surgical procedure is over.

The assessment needs to cover whether the patient is currently suffering from a psychiatric illness. The presence of psychiatric illness is not a contraindication for transplant per-se but would need to be addressed before the transplant, if possible. Solid-organ transplants have been possible for patients with severe mental illnesses like schizophrenia.[10]Active alcohol

use disorder in a patient with liver cirrhosis would make the potential recipient not suitable for a liver transplant, given the presumption that continued alcohol use after transplantation would be detrimental to the transplanted liver, leading to the futility of the entire transplant procedure. On the other hand, depression in a patient with progressive liver failure exacerbated due to the health condition might not be a contraindication to the transplant process. In fact, depression may resolve due to the improvement in the overall health of the recipient after the transplantation. Addressing patients with psychiatric illness during the waiting period may help to improve outcomes subsequently.

Assessment of the psychiatric illness in a patient who is planned for transplant may be made difficult due to the overlap of the symptoms of the medical illness and psychiatric disorder. Fatigue may be present in depression as well as could be due to heart failure. Similarly, autonomic symptoms may be present in anxiety disorder and also due to respiratory distress in patients who have respiratory failure and require lung transplantation. Discerning and differentiating symptoms may be challenging in such situations, and clinicians may need to rely onthe temporality of onset, course over time, persistence of symptoms, context of exacerbations (fatigue worsening with effort more likely due to medical disorder, while the relief of fatigue with mood improvement would suggest the same to be a part of the psychiatric disorder).

Assessment of previous psychiatric illness is important as there can be the recurrence of mental illness which can impact the overall management of the patient.For example, a patient with bipolar disorder may be asymptomatic, but re-emergence of manic symptoms or occurrence of a manic episode around the time of transplantation may complicate the picture. The potential recipient is likely to sleep less at that point in time, which may precipitate an episode. Ascertaining previous psychiatric illnesses (including substance use disorders) would help to optimize maintenance treatment and re-start treatment when warranted. The treatment regimen of psychiatric illness also needs to be considered carefully, as some of the medications may need to be stopped during the peri-transplant period, and some of the medications may have interactions with the immunosuppressants after transplantation.

Family history of psychiatric illness would provide some information of genetic vulnerability to psychiatric illness. Assessment of personality and coping can help to get an idea of how the individual would be able to deal with further stressors if they emerge. A detailed mental status examination should be performed, including higher mental functioning. Conditions like renal failure and liver failure which necessitate transplantation may be associated with neurocognitive impairments.

The assessment also provides a baseline for observing improvement or changes in cognitive profile, mood symptoms, and general adjustment to life circumstances. Whenever an opportunity arises, it might be prudent to get information from the transplant surgeon and other members of the team and discuss the findings of the assessment with them.A face-to-face discussion of the findings also gives an opportunity to clarify any doubts and provide more effective help to the transplant team.It is always better to have a conjoint session with the patient, their family and the primary treating team members to facilitate communication between the patient and the treating team and also bridging the communication gap. Many a times, patients being referred to the mental health professionals are not aware that they are being referred for pre-transplant evaluation, and also about the pre-transplant precautions and measures, actual transplant procedure, the impact of the transplant procedure on their way of living, cost involved in the transplant, duration of hospitalization, etc. In such a scenario, the mental health professionals have an important role in making the primary treating team aware about the lack of knowledge of the patient/family, and they should be

requested to provide adequate knowledge and address the queries of the patients/family. These can be done as part of the conjoint sessions.

Another situation encountered in clinical practice is evaluating a subgroup of patients who are referred for re-transplantation, especially for renal transplant. In such a scenario ascertainment of reasons for failure of the transplanted organ, time to failure, psychological reaction of the patient and the family members for the transplant failure need to be considered. If the organ failure is an outcome of the lack of adherence of the patient to the suggested recommendations, for example, use of alcohol in a patient who has undergone liver transplant, it may raise ethical issues of using scarce resources.

Documentation of the findings of pre-transplant evaluation is important. It provides a clear cross-sectional assessment of the patient's condition, and is useful for the transplant team. It can help to determine: (1) whether the potential recipient is suitable for transplant, (2) to understand if there are some psychiatric illnesses that may pose a challenge during the transplant process, (3) to plan the medications and become cognizant of potential drug interactions. Non-psychiatrists may not be very well aware of the psychiatric terminologies, and hence limited but rational use of jargon is preferred. For a potential transplant recipient, a typical final opinion, in case the potential recipient is found fit for transplantation, may read as *"Currently, there is no contraindication from Psychiatric point of view to suggest that X cannot undergo transplantation. However, a repeat psychiatric assessment must be done just prior to transplant"*.

Whether to use structured instruments for the assessment of the patient remains a prerogative of the evaluating psychiatrists. Some centers have devised their own processes of profiling patients and documenting their psychiatric status. Structured assessments can bea diagnostic instrument for making a psychiatric diagnosis, assess affective symptoms or general distress, neurocognitive functions, use of substances, assessment of personality and coping, and other instruments as deemed necessary. Table 3 presents some of the assessment instruments that can be used for the pre-transplant assessment of patients. The use of these instruments should not be considered obligatory, and clinicians can choose the instruments that they would like to use ina particular patient depending on the need and the comfort of the clinicians in using the same.

Pre-transplant psychiatric assessment can be conducted on more than one occasion. In case the patient is suffering from a psychiatric illness thatneeds to be addressed prior to the transplant, then appropriate treatment should be considered, especially if there is a reasonable gap between the initial assessment and the anticipated transplant procedure. In such a scenario, a re-assessment can be scheduled after a period of time when the psychiatric illness has been addressed. Also, gaps in information can be filled up in a re-assessment.

Table 3: Instruments that can be considered during the pre-transplant assessment of patients

Domain	Instruments
Diagnosis	Mini-International Neuropsychiatric Interview (MINI)
General assessment	General Health Questionnaire (GHQ)-12, K6 instrument
Depression	Patient Health Questionnaire (PHQ)-9, Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD)
Anxiety	Generalized Anxiety Disorder (GAD) Scale-7, Hospital Anxiety and Depression Scale (HADS), Hamilton Anxiety Rating Scale

	(HAMA)
Substance Use	Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Alcohol Use Disorder Identification Test (AUDIT)
Neurocognitive functioning	Mini-Mental Status Examination (MMSE), Hindi Mental Status Examination (HMSE), Montreal Cognitive Assessment (MoCA)
Personality	Eysenck Personality Inventory (EPI), Minnesota Multiphasic Personality Inventory (MMPI), IOWA Personality Disorder Screen
Coping	Brief Coping Orientation to Problems Experienced (Brief COPE) Inventory
Social Support	Social Support Questionnaire (SSQ), Multidimensional Scale for Perceived Social Support

Transplantation rating scales

Several rating scales have been developed for the assessment of candidates for solid organ transplantation.

The Transplant Evaluation Rating Scale (TERS)[11] is a clinician-rated instrument that looks at the adjustment of the patient on the basis of the evaluation of ten aspects of psychosocial functioning. The ten domains of psychosocial functioning are current or past mental disorders, personality disorder, substance use/abuse, compliance, health behaviors, quality of family and social support, history of coping, current coping with disease and treatment, quality of affect and, past and present mental/cognitive status. Each of these items is rated from 1 to 3 based on the level of impairment. The scale has been suggested to have good inter-rater reliability. It has been demonstrated to be a good instrument for the pre-transplant assessment of patients undergoing a liver transplant, kidney transplant, and lung transplant.

The Psychosocial Assessment of Candidates for Transplantation (PACT)[12]has 8 subscales, and each of them is rated on a 5-point Likert scale from 0 (poor candidate) to 4 (good candidate). The rating is clinician determined. The 8 subsections include 8 subsection items: family availability, family support, the risk for psychopathology, personality factors, ability to sustain change, medical adherence, drug and alcohol abuse, and relevant knowledge. This instrument has been used for several solid organ transplant candidates and also has been utilized in pediatric transplant recipients.

Yet another commonly discussed instrument is the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT).[13] This instrument is also rated by the clinicians and has 28 items covering various issues like understanding of the patient, treatment adherence, lifestyle-related factors, substance abuse, social support, psychological stability, and psychopathology. The questions are scored on Likert scales, and each of the questions has a different weight. Based on the total scores, the interpretation is provided, and the candidate is considered as an excellent candidate, good candidate, minimally acceptable candidate, poor candidate, and high-risk candidate.

For pediatrictransplant candidates, a separate instrument, Pediatric Transplant Rating Instrument (P-TRI), has been developed.[14]The instrument assesses 17 psychosocial factors divided into seven factors: illness factors, treatment adherence, patient or parental substance abuse, patient or parental psychiatric history, family environment, relation with medical team, and financial, logistical, and psychosocial support. The inter-rater reliability ishigher for the pre-adolescent application of the scale rather than adolescent application.

Psychosocial Assessment

Several psychosocial issues affect the transplant procedure, and the psychiatrists are expected to be cognizant of the same .[5,15]Some of these psychosocial issues are presented in table 4. These have a bearing on the management of the patient (including psychiatric management) and may lead to differences in outcome of transplant.

Table 4: Psychosocial issues with transplantation of relevance to the psychiatrist

Psychiatric disorders
Personality issues
Substance use
Adherence to medications
Financial stressors
Work and vocation
Familial concerns and social support

Psychiatric disorders can be present in the individual who is receiving the transplant, either before the surgery or afterward.[6,16] The profile of the psychiatric disorder can be varied, ranging from stress-related disorders to psychotic and mood disorders. The psychiatric evaluation is not aimed to exclude patients per-se, but to help the patients as well through the treatment. Many of the psychiatric disorders can be treated effectively in patients who are supposed to undergo solid organ transplantation.

Some personality issues can be of relevance in patients who are undergoing transplants. Cluster A and anxious-avoidant personality traits may interfere with treatment-seeking, and patients may not engage with the treatment providers. Patients with paranoid personality may be suspicious of treatment providers and may check the treatment regimen carefully. Patients with dependent personalities may depend on the family members or treatment providers for making the decisions for them and may not effectively participate in the decision making. Patients with antisocial or narcissistic traits may have difficulty following suggestions of the transplant team. Thus, understanding the personality of the potential recipients is important.

Many individuals consume substances in a non-dependent pattern. Active substance use (particularly alcohol and tobacco) is generally seen as a contraindication for being considered for transplant surgery. Smoking can result in delayed wound healing and reduced efficacy of medications. While individuals consuming substances can be helped with treatment, many potential transplant recipients may not disclose their consumption status, thinking that they may be rejected from transplant lists. Occasional consumption of substances is not a contraindication to transplant, and transplantation has been carried out on individuals who have been using substances in the past.[17] However, the ethical consideration of justice implores that scarce human organs should be judiciously used. In general, for patients with alcohol dependence syndrome, abstinence from alcohol for 3-6 months is required for being considered for the organ transplantation, with the exception of the life-threatening conditions.

Post-transplant, patients need to adhere to the medications so that graft rejections do not occur. Advances in immunogenetics and pharmacotherapy have led to the use of immunosuppressants with minimal side effects. Yet, the patients are required to take these medications on a long-term basis. Lack of adherence to these medications can be due to various reasons, including increasing age, a higher number of comorbidities, lower social

support and employment, lower education, forgetting to take at the correct time, manifestation of depression, rebellious behavior, intolerance of side effects, poor rapport with the treatment time, and others.[18,19]In the Indian context, financial issues may also be one of the contributing factors for poor medication adherence. The role of the psychiatric assessment may also be to understand the reasons for such non-adherence and guide further measures to address it.

The process of organ transplantation and consequent medications can be quite draining for the patient and the family members. This is often a concern and a source of stress to the individual. This may not be very explicitly expressed but may play a role during the decision-making process of consideration of transplant, around the period of surgery and subsequently as well.

After the transplantation, the patient may not be able to resume the previous vocation in the manner he/she used to do before the surgery took place. The patient may need to curtail the exertion and social interaction during the course of the recovery. This may lead to issues in rehabilitation or resumption of vocation. Purposeful engagement, which may help in re-building resilience, may thus be affected due to the constraints after the transplant procedure.

Family support plays an important role in the entire process of transplantation. During and after the transplant, the individual becomes dependent on others to some extent. Identification of familial and other social supports for such a time is always helpful. The family and social support help in providing care, pragmatic support, and also humane touch that helps an individual to cope with difficult situations.

Assessment of the donor

Assessment of the live donor is also an important component of the pre-transplant evaluation. Live donors are applicable for liver and kidney transplantation among solid organ transplantations. Generally, live donors are the immediate family members of the recipient. Swap donors are also permitted wherein two or more sets of donors and recipients swap organs in view of ABO compatibility. Many donors consider organ donation a satisfying experience that givesthem a sense of purpose.

The pre-transplant assessment of the donor shares many of the characteristics of the assessment of the recipient (Table5 and figure 4).The identity of the donor can be checked by looking at the identification cards issued by various government agencies (Aadhar Card, Voter ID, Driving license, Passport, etc), marriage certificate (in the case of spouse), and past photographs of the donor with the potential recipient.The intake interview, after confirming the identity and noting the informants, encompasses needs to elicit what the potential donor knows about the transplant procedure and the risks involved in it. The competence of the potential donor needs to be checked. One of the major aims is to assess whether there is any coercion involved, and if so, what is the degree of coercion if it is applicable. Coercion may be manifest or subtle, and some degree of influence does occur in the decision making. Whether the influence is to the degree that constrains autonomy has to be judged on case to case to case basis.The reasons/ motivation for becoming the donor should also be discussed. Often, multiple family members are considered for donation, and the selection of the final donor has some degree of pressure or a feeling of obligation to volunteer for organ donation. Sometimes, family dynamics play a role in deciding who would become the donor, and it may not be clear whether the potential donor is coerced or wants to donate out of compassion. A ‘black sheep syndrome’ has been described wherein a rather disrespectful family member attempts to get recognition and admiration of the family by becoming the donor. Further, many a times, there could be financial disparity between the different family

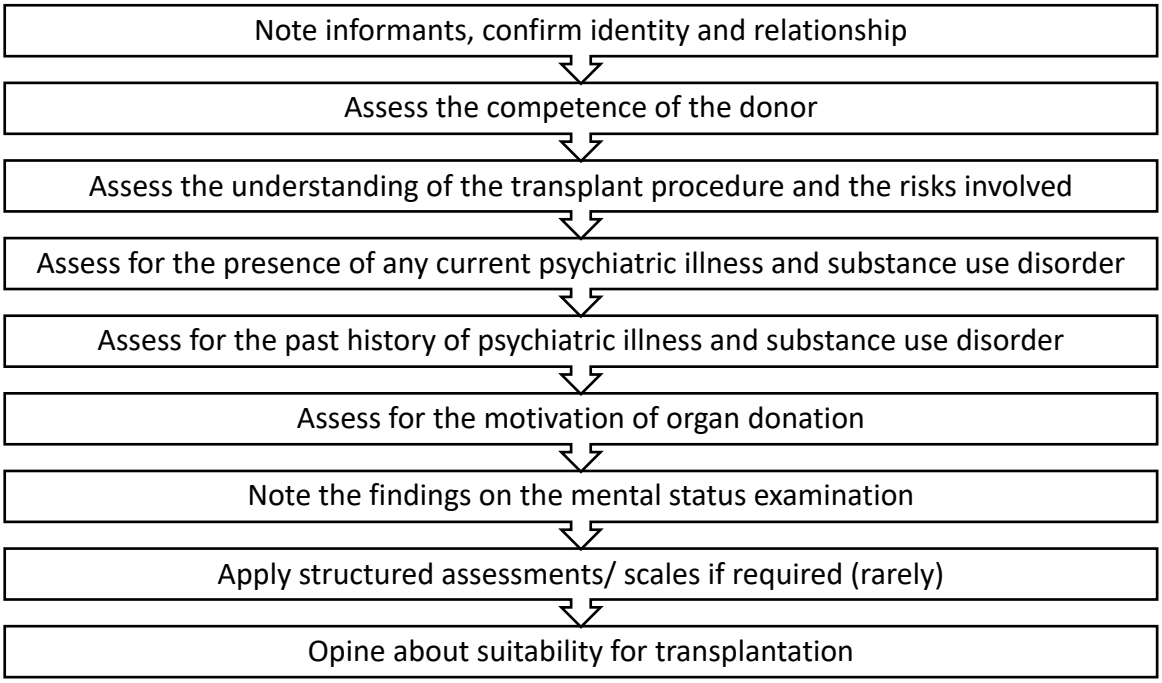
members, especially the siblings. In such a scenario, it is important to assess the aspect of any financial transaction or obligation on the part of the donor towards the family of the recipient. Another aspect to note in the Indian scenario is donation of the solid organs by the female spouse to her husband. In majority of the solid organ transplantations in India, females are the donors (add reference). Hence, while evaluating the spouse it is important to assess the association of the onset of the physical illness with the duration of marriage, overall duration of marriage, number of children, and pressure from the other family members on the spouse to donate the organ. It is often useful to inform the spouse that he/she is not obliged to donate the organ, if he/she does not wish to do so.

The assessment of the donor should evaluate for the presence of a psychiatric disorder or substance use disorder. The presence of a psychiatric disorder by itself is not a contraindication for organ donation provided competence is established. However, if time permits, then addressing the psychiatric disorder to the extent possible would be helpful in such a situation.In general, persons with intellectual disability are not considered for becoming a donor.The findings of the mental status examination should be noted, especially cognitive assessment. For persons having minimal cognitive impairment, mental competence to consent for the surgery is important.If the potential donor is found to be competent, then he/she should be considered for transplantation.Structured assessment of symptoms of anxiety, depression, and distress is rarely necessary for the potential donors. Table 3 presents some of the questionnaires that can be used for the assessment of the donors as well. The final impression of the suitability for being a donorshould be opined about. Should we have both table and figure with same content?

Table 5: Pre-transplant assessment of the donor

Note who all provided the information
Confirm the identity of the donor, and the relationship with the recipient
Assess the competence of the donor
Assess the understanding of the transplant procedure and the risks involved
Assess for the presence of any current psychiatric illness, including substance use disorder
Assess for the past history of psychiatric illness, including the substance use disorder
Assess for the motivation of organ donation
Note the findings on the mental status examination
Apply structured assessments/ scales if required (rarely)
Opine about suitability for transplantation

Figure 4: Pre-transplant assessment of donor



Ethical considerations for psychiatrists

Organ transplantation raises some ethical issues as well.[20–22] One of them is autonomy. The principle of autonomy mandates that the prospective patient must have a free choice to decide whether he or she would like to get a transplant. Some degree of coercion or influence maybe there as the person with the failing organ may be suggested by family members and friends to undergo the transplant. However, the final decision whether to undergo the transplant or not resides with the patient. If the patient is incompetent or a minor, then the guardian or legal representative can decide for the person undergoing the solid organ transplant. The principle of autonomy also applies to a considerable degree for the donor as well. The donation of organs is a voluntary choice, and the treating psychiatrist should clearly mention when he/she finds that the donor may not be having an autonomous choice.

A major ethical issue in the field of organ transplantation pertains to the facet of justice. When organs for transplant are scarce, the tenet of justice calls for equitable distribution of the organs without favor. This particularly applies to cadaveric donors. The window of opportunity for transplant is short, and the organ has to be quickly transported, sometimes across cities, to reach the recipient who undergoes the transplant procedure immediately. Many countries have national lists of potential organ recipients, and the organs recipients are identified on the basis of such lists. India does not have such a consolidated list as of now. Another aspect of justice is deciding whether to transplant organs where the prognosis is relatively poor, vis-à-vis where the prognosis is expected to be better.

The ethical principles of beneficence and non-maleficence applyas in any other case. The psychiatrists and transplant team members act in the best interest of the patients who are to receive the transplant. Such a principle of beneficence extends on to the donors as well, and their health also needs to be taken care of appropriately. The practice of non-maleficence suggests physicians do no harm, i.e.,avoid transplantation in situations that may worsen the quality of life without actually benefitting the patient in terms of longevity.

The legal framework of transplantation in India

In India, the transplantation of solid organs is governed under the Transplantation of Human Organs and Tissues Act (1994). The Act was further amended in 2011.[23–25] The Rules

alongside the Act came in 1995 and were further revised as Transplantation of Human Organs and Tissues Rules, 2014. The Act has been promulgated to streamline the process of organ donation and transplant activities. The introduction of the Act in 1994 led to the acceptance of brain death as a form of death. The Act also prohibited the sale of organs for transplantation.

The Act clarifies who can donate the organs. For living donation, father, mother, brothers, sisters, daughter, son, spouse, and grandparents can donate provided they are able to show the proof of relationship by genetic testing and/or by legal documents. If there are no eligible first-degree relatives, and if there is a donor who is willing to donate the organ, then the recipient and donor are required to seek special permission from the government-appointed authorization committee. They are subsequently asked to appear for an interview in front of the committee. The committee evaluates that the motive of donation is altruism or affection and not a financial inducement or other types of coercion. A mental health professional may have to ascertain the level of altruism for the donor, by reviewing his personality traits. For brain dead donors, the Act mandates that two certifications are required 6 hours apart by two different doctors nominated by the appropriate authority, and at least one of them should be an expert in the field of neurology. For dead donors, organ transplantation is possible if the person had authorized removal of organs from the body after the death signed in front of two witnesses on a prescribed form. If the donation has not been committed prior to death, then the legal guardians of the person can provide consent for organ donation of the person being who has become brain dead. For brain-stem dead individuals, transplantation is carried out after a certificate is signed by all members of the Board of Medical Experts, and when the individual is less than 18 years of age, additional signed consent of the parents is needed.Approval of Authorization Committee is required when considering transplantation when either donor or recipient is a foreign national.

Authorization committees are formed under the Mandate of the Transplantation of Human Organs and Tissues Act. They are six-member teams and can be hospital-based (where transplantations are carried out) or state or district-level committees. The medical practitioners in the Authorization Committees are not part of the transplant teams. The Authorization committees examine the request for organ transplantation and then decide upon whether the transplantation should be allowed in a particular case or not.

The psychiatric assessment may be required by the Authorization Committee when unrelated donors and recipients are being planned for organ transplantation. This may be more applicable in cases of a donor/recipient being a foreign national.

Table-6: Basic facts about Transplantation of Human Organs and Tissues Act (1994)

Who can donate: Father, mother, brothers, sisters, daughter, son, spouse, and grandparents
What if the first degree relatives are not available: Recipient and donor are required to seek special permission from the government-appointed authorization committee. It needs to be ascertained that there is no coercion and financial exchange for the transplant (in such a scenario, the mental health professional may have to ascertain that the donor is doing so altruistically, and the same may have to be ascertained)
What about cadaveric donor: Two certifications are required 6 hours apart by two different doctors nominated by the appropriate authority, and at least one of them should be an expert in the field of neurology to ascertain brain death. The cadaveric donation can be considered if the person has pledged for the same before death or if the legal guardians consent for the organ donation

Psychiatric assessment in immediate peri-transplant period

In the immediate peri-transplant period, the psychiatric assessment may be catering to several issues, like: (1) whether the potential recipient is still competent for transplant, (2) whether there are any immediate psychiatric problems that need to be addressed, (3) addressing post-transplant delirium, and (4) addressing immediate post-transplant psychological reactions.

The psychiatrist may be called in if the patient is apprehensive about the transplant procedure. The psychiatrist may be able to comment on whether the patient is still competent for the intended surgery. Also, any anxiety or apprehension of the patient can be attended to during such a psychiatric consult. In case the patient rejects the transplant outright, then again, competency should be checked, and the transplantation be withheld till the patient consents to. If the patient becomes incompetent, and in the presence of explicit instructions of the patient for the conduct of surgeryprior to him/her becoming incompetent, the surgery should be undertaken.

Delirium or acute confusional state may occur in the patient prior to the transplant or subsequent to the transplant. The reasons for such delirium can be many, including failure of the organ, medication adverse effects or interactions, dyselectrolytemia, and infections. Often multiple etiologies interact to produce delirium. Assessment in such situations focuses upon the clinical diagnosis of delirium. Confusion Assessment Method (CAM) or Confusional Assessment Method for Intensive Care Unit (CAM-ICU) are quick bedside assessment instrument for delirium. Instruments like Delirium Rating Scale-Revised 98 version (DRS-R98), full version of the CAM, or CAM-ICU can be used to quantify the extent of delirium. Delirium can be hyperactive, hypoactive, or mixed. Often, hypoactive delirium is missed clinically as the patient is not disruptive. Yet, such a delirium should also be addressed. Management of delirium focuses on the identification of the cause of delirium and addressing the cause as promptly as possible. Antipsychotics can be helpful in reducing the aggression associated with delirium. Benzodiazepines are generally avoided as they lead to prolongation of confusion. Non-pharmacological measures like reorienting, placing the patient near the window, having a clock in intensive care, meeting with family members may all help to reduce the symptoms of delirium and make the patient more amenable (Add the reference of IPS Delirium Guidelines). The psychiatrist needs to consider carefully the drug interaction between medications given for the symptoms of delirium and the medical condition/ other medications being given to the patient. For example, hepatically metabolized antipsychotics like risperidone and haloperidol need to be carefully given in patients with hepatic failure. Renally excreted antipsychotics like amisulpride would need to be carefully considered in a patient with renal failure awaiting transplant.

In the immediate post-transplant period, the patient may feel overwhelmed, leading to symptoms of acute stress reaction, adjustment disorder, or depression. Assessment for such a patient may include evaluation for depression and clarifyingthe presence of cognitive deficits. Such an assessment also provides an opportunity to provide supportive therapy to the patient and nudging the patient to focus on problem-solving and using his/her strengths in dealing with the challenging situation.

Post-transplant psychiatric assessment

In the post-transplant period, psychiatric assessments are generally initiated, when the transplant team suspects that there may be a comorbid psychiatric disorderhindering the improvement of the patient, or when the patient fails to maintain adherence to the treatment

provided (mainly the immunosuppressants), or when hostilities emerge between the patient and the treatment providers.

After the transplantation, there can be a recurrence of a psychiatric problem or the emergence of a new psychiatric diagnosis. It has been seen that depression may affect up to 60% of the solid organ recipients and is associated with increased rates of mortality and development of neoplasms in the post-transplant period. Addressing psychiatric disorders that occur after transplantation is thus important to improve the outcomes of the patients. Several challenges are present when the patients with transplantation present with symptoms of psychiatric disorder: (1) whether the symptoms are severe enough and are causing impairment to be considered as a disorder, (2), whether the symptoms are due to the psychological reaction of the patient or are due to the ongoing medications; (3) whether to wait for spontaneous resolution of the symptoms (especially if they are related to temporary adverse medical outcomes) or start treatment immediately, (4) what kind of treatment(s) to offer (psychotherapy versus pharmacotherapy), and (5) how to avoid or minimize the drug interactions; (6) what would be the impact of the addition of psychotropics on the physical health of the patient (for example, risk of hyponatremia and bleeding while using selective serotonin reuptake inhibitors (SSRIs); risk of QTc prolongation while using psychotropic with other medications or in patients with hypokalemia), and (7) other medication associated side effects which can impact the quality of life of the patient. It might be difficult to establish the diagnostic threshold, especially the impairment criteria. This is because the patient might have had social or occupational impairment already imposed by the medical condition that led to the transplant.Yet, a decrease in social interactions or work productivity in an individual who had regained many of these functions may hint towards a psychiatric diagnosis. Patients who have undergone transplantation may be frail, limited in mobility, or otherwise unwilling to travel. Regular sessions of office-based psychotherapy maynot be suitable for the same. Online psychotherapy may be considered favorably in such cases. Medications, when offered, should be started in lower doses, and dose escalation should be done cautiously with appropriate monitoring (for example reviewing the serum electrolytes while using SSRIs). Among the antidepressants, escitalopram and sertraline are preferred as they are less frequently associated with drug interactions. For cases of alcohol use disorder where even non-dependent use of alcohol during the post-transplant phase occurs, it might be important to act early and prevent further drinking to avoid injury to the transplanted liver.

Apart from psychiatric disorders, psychiatrists may be required to evaluate in cases when the patient refuses treatment. Poor adherence to the medication regimen (immunosuppressants, antibiotics, etc.) may lead to graft rejection. Hence, enhancing the motivation of the patient to continue with the medication in appropriate doses would be helpful. Assessment by the psychiatrists focuses on the reasons for non-adherence to medications, critically examining for the presence of depressive disorders (hopelessness and wish to die), psychosis (suspiciousness towards the treating team and the medications), neurocognitive impairment (forgetting medication regimen or getting confused about the medicines), and substance use disorders. In case any psychiatric disorder is identified, then the patient can be suitably managed. The psychiatrist can also suggest measures like reminders, positive reinforcement by appreciating the efforts of the patient and paying attention to the patients' concerns, which may help to address the issue of adherence.

Psychiatrists may also be called in during the post-transplant period when there are communication issues or explicit hostilities between the patient and the treatment team. Personality differences and individual circumstances can result in a rift between the patient and the treatment providers. An aggressive (even verbal) stance of the unsatisfied patient results in doubts in the minds of the treatment provider whether the patient is suffering from a

psychiatric illness. In such a situation, the assessment bythe psychiatrist should focus on ascertaining the presence of a psychiatric illness (like psychotic disorder, mania, delirium, dementia, or personality disorder). If a psychiatric disorder seems to be contributory to the situation, then it should be addressed. In case a diagnosable psychiatric disorder is not present, but personality traits are identified, then further management would focus on improving communication and engagement with the transplant team. The psychiatrist may like to understand the point of view of the patient and the treatment providers, and attempt to improve the communication between the two. The psychiatrist may be able to guide the patients about what is expected of him/her during the treatment process. The psychiatrist may also be able to help the treatment providers understand the patient's point of view and what measures would result in fewer conflicts in patients with certain personality traits.

Conclusion

To summarize, psychiatric assessment of potential recipients and donors (when applicable) isan important step in the pre-transplant evaluation. The pre-transplant assessment encompasses the recipient's understanding of the transplant, any known psychiatric illness, relevant family history, and current mental status examination.Similarly, the donors should be assessed for their understanding of the procedure and risks involved, motivation for organ donation, psychiatric history, and current mental status examination. Psychiatric assessments can also be requested immediately after the transplant surgery, primarily for delirium. During the subsequent follow-up period, the assessment may need to focus on the issues of adherence, the emergence of psychiatric illness or substance use, or any interpersonal relationship issues. The psychiatric assessment also needs to consider the psychological, social, cultural, and economic attributes of the patient. Assessments should be documentedand discussed with the transplant colleagues when an opportunity arises.

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Clinical Practice Guidelines: Management of patients in intensive care units.

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1. Introduction

Since the birth of intensive care medicine in 1953 psychiatrists have played increasingly important role in providing services to patients in ICUs. A paper published in JAMA as early as 1965 is one of the first documentation of psychiatric consultation in ICUs.[1]

Significance of the topic is underscored by high prevalence of psychiatric disorders in ICUs, which ranges from below 20% to above 60% according to the type of ICU and assessment methodology [2] and includes various organic brain disorders and other psychopathology.

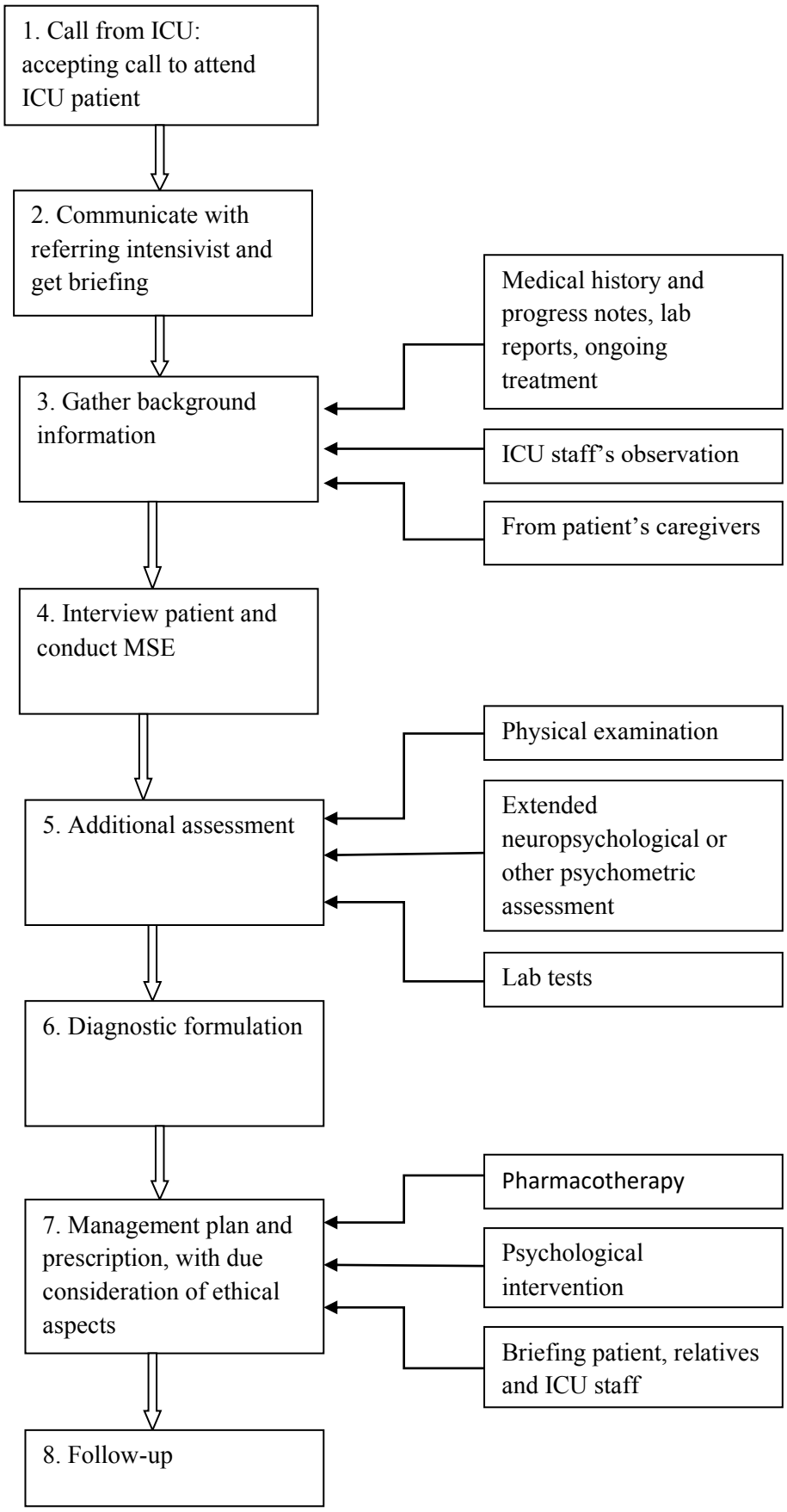
2. Scope

Objective of the current guidelines is to provide recommendations to psychiatrists and critical care teams, and scope includes:

- Management of psychiatric problems in ICU patients
- Management of psychiatric emergencies arising out of
    - Suicide attempt
    - Complications related to alcohol and substance use
    - Toxicity / complications related to psychotropic medications
- Addressing ethical issues, capacity assessment for informed consent for procedures, etc.
- Sensitivity to stress and burn-out issues in ICU team

A general approach of psychiatric consultation in ICU is presented first (figure 1). Assessment and management of commonly encountered and important conditions for which psychiatric referrals are made in the ICU is elaborated thereafter.

3.0. General approach of Psychiatric Consultation in ICU: Figure 1



3.1 Call to psychiatrist from the ICU – accepting call to attend ICU patient

By definition, ICU is the place for treatment of the critically ill who deserve to be attended on priority. Paper / EMR notification is often accompanied by verbal / telephonic notification, and serves to communicate acceptance of the call to attend the ICU patient. The degree of urgency to attend the call is generally communicated by the referring ICU team, and depending upon the setting the first responder could either be a psychiatry resident or consultant, and reporting/escalation protocol is expected to be in place in case of residents attending the call.

3.2 Communication with referring intensivist and getting briefing about the case

Communication with the referring intensivist, either during the referral call or at a subsequent opportunity, provides important opportunity to get briefing about the case including the specific reason for referral. Organic brain disorders top the list of referrals followed by suicide attempts and anxiety / depression. [3]

Table 1: Diagnostic break-up of psychiatric referrals in ICU

Diagnosis	% of cases
Organic mental disorders	
Alcohol related disorders	14.56
Organic brain syndrome	19.09
Total	33.65
Suicide attempts	32.69
Anxiety disorders	12.94
Depressive disorders	06.80
Psychotic disorders	03.24
Other psychiatric illness	09.06

*Adapted from Bhogale GS et al[3]

3.3 Gathering background information

Upon entering the ICU, it is prudent to obtain all the relevant information about the case available from different sources viz.

- Medical records – which contain information such as case history and physical examination notes, chart of vitals, reports of laboratory investigations, medical diagnosis, ongoing treatment and interventions, progress notes, and record of behavioural abnormality, etc.
- Since patient relatives have limited physical presence in the ICU, nursing staff and resident doctors in the ICU are important source of direct behavioural observation. It is therefore fruitful to spend few minutes interacting with them in addition to reviewing the medical record.

- Patient's caregivers are useful source of prior medical and psychiatric history and treatment, events leading to the ICU admission, and course in the ICU including patient's behavioural response.

Importance of gathering detailed background information is highlighted by the fact that ICU patients may not be in a condition to provide much details by themselves.

3.4 Interviewing ICU patient and conducting Mental State Examination (MSE)

- Interviewing ICU patient / conducting MSE is a skilled task. Psychiatrist needs to be swift in conducting the mental state and other bedside examination without unduly stressing the patient. Availability of rich background information is therefore very helpful.

- Barriers in conducting interview / MSE may include difficulty in comprehension / difficulty in expression or low level of alertness on account of either medical condition or effect of medication. Initial assessment focuses on making quick judgement about the extent to which verbal assessment can proceed, and careful behavioural observation plays very important role in the overall assessment of clinical condition.

3.5 Additional assessment

- Physical examination: ICU patient's general and systemic physical examination including neurological examination findings recorded in case notes are available to psychiatrist for review, who should however conduct any such examination that may be indicated at the time of attending the call.

- Additional assessment may include extended neuropsychological assessment or specific scales over and above bedside assessment of MSE. These assessments can be carried out either by the psychiatrist or any other trained personnel.

- Additional laboratory tests can be ordered to consolidate the clinical impression and to aid the management, and may include biochemical tests (such as drug levels), electrophysiological tests (such as EEG), or brain scan (such as MRI).

3.6 Diagnostic formulation

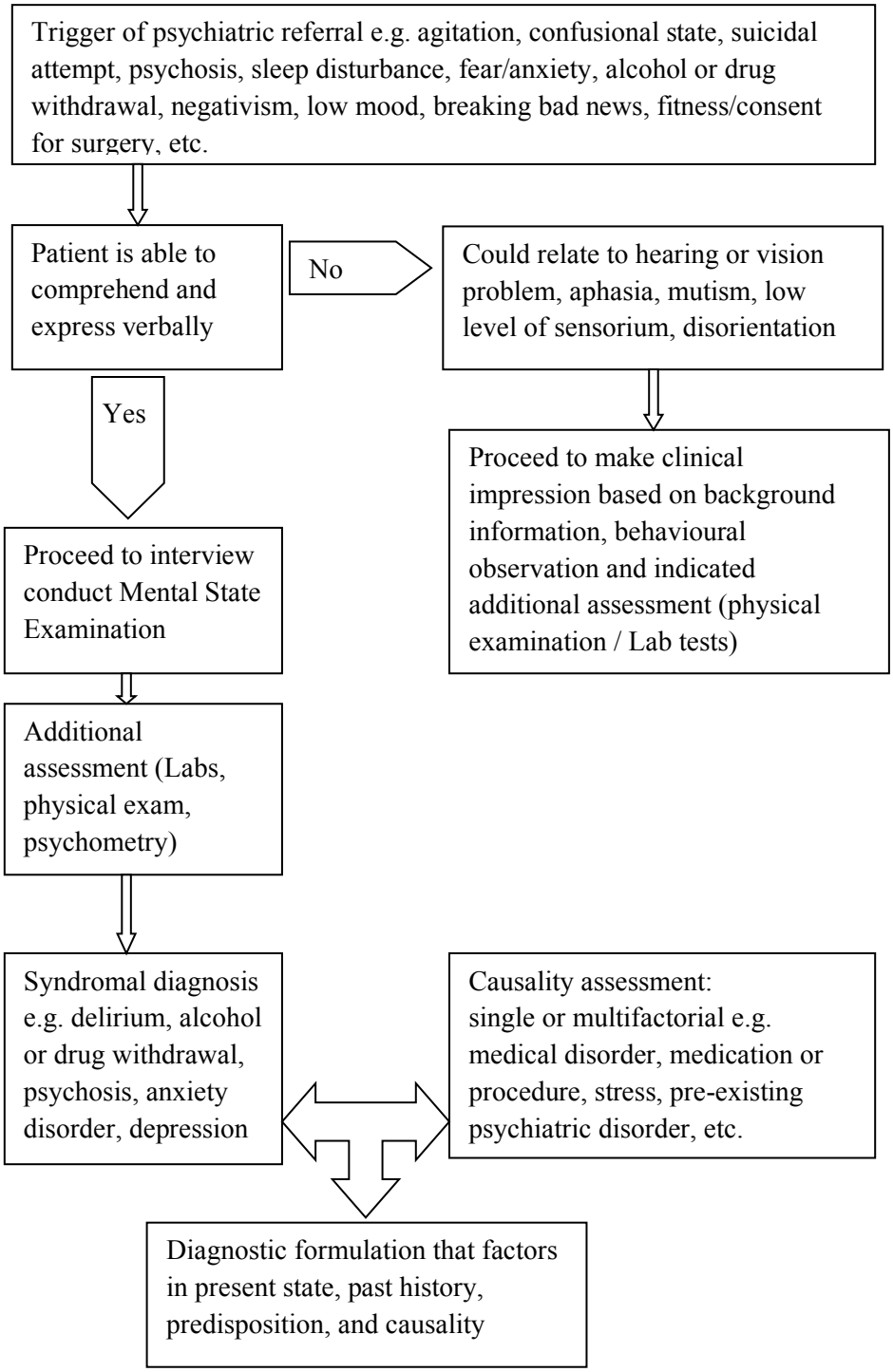
- Diagnostic formulation includes syndromal diagnosis and ascertainment of causality.

- Formal classification like the International Classification of Diseases (ICD) system (current 10^{th} version, and soon to be introduced 11^{th} version) provides clinical descriptions and diagnostic guidelines.

- In terms of causality, the psychiatric syndrome/disorder may either be linked to the medical illness or its treatment, or attributable to the stress of illness and environment, or a primary psychiatric disorder including alcohol and substance use.

- ICU stay itself could be very stressful. Patients in the ICU experience physical and psychological stress related to the serious and often life threatening illness, which is compounded by aspects of ICU environment like frequent movement of staff, noise of machines, masking of zeitgebers, restrictions on patients regarding mobility and communication, and being witness to adverse outcome of other patients; weakness, fatigue and cognitive impairment may have additive effect.

Decision process leading to diagnostic formulation: Figure 2



3.7 Management plan and prescription, with due consideration of ethical aspects

- Very often quick mitigation of the index behavioural disturbance is expected from the psychiatric referral. However, choice of pharmacotherapy including the agent, dose and route of administration warrants careful consideration of :

  - Medical context e.g. compromised hepatic, renal or cardiac status, presence of electrolyte disturbance, history of seizures, etc.
  - Ongoing medication e.g. anticoagulants, concomitant medications which can interfere with metabolism of psychotropic agents, and drug-drug interactions, etc.
  - Possibility or otherwise of administration through the oral route.
  - Careful dose titration as per medical status of the patient to maximise therapeutic benefit and minimize possibility of adverse effects like excessive sedation, anticholinergic side effects, QTc prolongation, etc.
  - In case of ongoing psychotropic medication for pre-existing psychiatric condition, decision needs to made either to hold temporarily or stop permanently, to continue or to modify the agent and dose keeping in mind the context and various safety issues mentioned above.

- Psychological intervention, especially supportive counselling, as permitted by patient's present state, is helpful in alleviating fear, anxiety, and stress associated with the illness and with ICU milieu.[4]

- Briefing ICU staffs about the anticipated response of psychiatric intervention, about watching out for any adverse response and prompt reporting of the same are important steps to ensure quality care. If any PRN prescription is made, it best to specify the situation which should trigger its use.

- Briefing patient relatives about the psychiatric intervention being prescribed is equally important, especially considering the fact that many ICU patients may be in a vulnerable condition unable to consent in true sense. However, due care should be taken to protect confidentiality of patient narrative, particularly when patient has indicated so, as is often the case in suicide attempt.

- Being the place of treatment of critically and terminally ill patients, ICU is also the setting of several ethical dilemmas and considerations which may range from physical procedures like application of restraints, to psychological procedures like breaking bad news, preparation for end of life situation and helping relatives make difficult decisions like taking patients off life support, and facilitation of advance directives. Family satisfaction is related to clinician communication.[5] It could also be the setting to detect foul play and protect the patient, and to encourage altruistic actions like organ donation. COVID-19 situation has generated debate about the role and limitations of tele-consultation for ICU patients.

- It needs to be appreciated that family members may also find the situation challenging and experience depression, anxiety, or anticipatory grief, and deserve to be supported as per the need. Prevalence of PTSD risk is 16-21% during 6 months post-

discharge[6],[7], and relatives can be made aware about availability of psychiatric help should they need it.

3.8 Follow-up

- No quality management plan is complete without follow-up. The frequency of follow-up is often mutually worked-out between the intensivist and the psychiatrist, and may include post-discharge visits for continuation of psychiatric intervention.
- A recent review and meta-analysis of 48 studies revealed that the point prevalence of PTSD symptoms in patients who received ICU care ranges from 15% to 20% during 3 to 12 months post-discharge [8] and psychiatrist should be vigilant for timely management of the same. Cognitive dysfunction, particularly after delirium, is also a common sequel (17 to 78%) which may persist for up to several years but tends to improve over time [9] and it is prudent to screen as a routine on the follow-up visit.
- Depending on the nature of the case attended in the ICU (e.g. suicide attempt or alcohol withdrawal) and as per the discretion of the psychiatrist, optional sharing of tele-contact may be helpful for prompt cognizance of any problem post-discharge pending the scheduled follow-up.

Assessment and management of common and important psychiatric conditions inICU:

4.1. Delirium

Delirium is the commonest organic/neuropsychiatric disorder caused by transient disruption of normal neuronal activity secondary to systemic disturbances. Risk factors of delirium include older age, dementia, hypertension, emergency surgery or trauma, mechanical ventilation, metabolic acidosis, APACHE II score and coma; multiple organ failure poses moderate risk.

A systematic review of 42 studies involving 16,595 patients found the incidence of delirium 31.8% in critically ill patients, and even higher in ICU setting ranging from 60-87% in medical ICU and up to 89% in survivors of stupor or coma. Incidence in common surgical condition like hip-fracture is 34% to 92%.[10] However it remains under diagnosed and under referred, possibly due to difficulty in recognition by the ICU staff at the extreme of symptom presentation. An Indian study found that the prevalence rate in medical/surgical ICU was 68.2% however referral rates to psychiatric team was 1.7%.[11]

In terms of outcome, delirium is associated with increased morbidity and mortality, increased incidence of hospital-acquired complications, prolonged hospital stay, poor functional and cognitive recovery, and decreased quality of life in addition to increased cost of care and burden to caregivers. Recognising its significance, Clinical Practice Guidelines for Management in Elderly was brought out by Indian Psychiatric Society in 2018[12] which provides details of various aspects of management. A brief overview and update is provided for ready reference and to supplement these guidelines.

4.2. Clinical presentation:

Delirium is characterized by acute onset of fluctuating cognitive impairment (disorientation, memory disturbance) and a disturbance of consciousness / awareness with reduced ability to attend (focus, sustain and shift attention), which is frequently associated with perceptual abnormalities, sleep–wake rhythm dysregulation, disorganized thought process, emotional dysregulation, and abnormal psychomotor activity. A prodromal phase consisting of restlessness, sleep disturbance, anxiety and irritability may precede by few hours or days. Following Delirium phenotypes are recognised[13]:

- Subsyndromal type
- Hypoactive delirium and its extreme, the catatonic subtype
- Hyperactive delirium and its extreme, the excited subtype
- Mixed type
- The protracted or persistent type

Hypoactive type is the commonest (65%) and often under-recognized.

4.3. Pathophysiology:

Systems integration failure hypothesis about development of delirium integrates precipitant factors, delirium substrates and clinical factors as a cause for acute brain failure leading to specific delirium phenotypes and its associated outcomes. Deficiencies in acetylcholine and melatonin, excess of dopamine, norepinephrine and/or glutamate and variable alterations in 5-hydroxytryptamine or serotonin, histamine and/or gamma-aminobutyric acid are linked to delirium.[10]

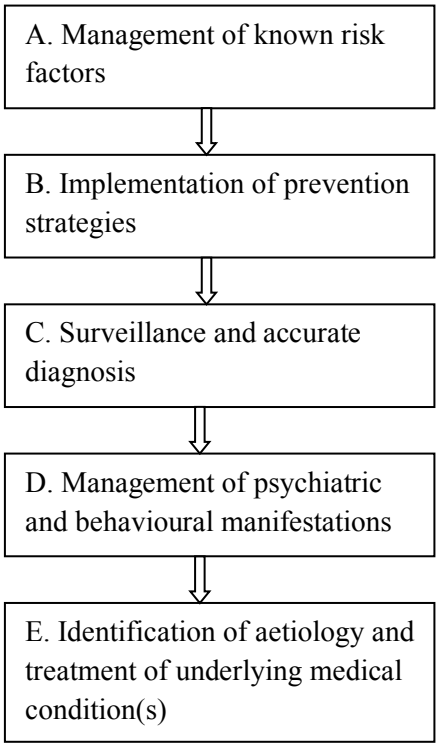
Table 2: Pathophysiology of Delirium

Precipitant factors	Delirium substrates	Clinical factors
Infection	Neuronal aging	Neurotransmitter dysregulation
Trauma	Neuroinflammation	Network disconnectivity
Surgery	Oxidative stress	
Hypoxia	Neuroendocrine dysregulation	
Medications	Circadian dysregulation	
Metabolic derangement		
Substance abuse		
Organ failure		

*Adapted from Maldonado, J. R.[13]

4.4. Assessment and Management of delirium:

Five Steps: Figure 3



4.4.A. Management of known risk factors of delirium:

Though older age, cognitive impairment, medical illness and pre-existing brain disorders are non-modifiable, several risk factors could be modifiable viz. various pharmacologic agents, especially GABA-ergic and opioid agents, and medications with anticholinergic effects, prolonged and/or uninterrupted sedation, immobility, acute substance intoxication, substance withdrawal states, use of physical restraints, water and electrolyte imbalances, nutritional deficiencies, metabolic disturbances and endocrinopathies (primarily deficiency or excess of cortisol), poor oxygenation states (eg, hypoperfusion, hypoxemia, anaemia), disruption of the sleep-wake cycle, uncontrolled pain, etc.

Table 3. Risk Factors for delirium

Potentially modifiable risk factors	**Nonmodifiable risk factors**
Sensory impairment	Advancing age>65 years
Immobilization	Cognitive impairment
Medications, polypharmacy	Multiple comorbidities
Acute neurological diseases such as acute stroke, intracranial haemorrhage, meningitis, encephalitis	History of delirium, stroke, neurological disease, falls, or gait disorder
Acute illnesses such as infection, dehydration, fracture or trauma, HIV	Chronic renal or hepatic disease

infection	
Metabolic derangements	
Surgery	
Environment	
Pain	
Emotional distress	
Sustained sleep deprivation	

*Adapted from T.G. Fong[14]

4.4.B. Delirium prevention strategies[13]:

Considering significant negative consequences, prevention of delirium assumes utmost significance. It has been listed as one of the six most common preventable conditions among hospitalized elderly patients.

Both pharmacologic and non-pharmacologic strategies of delirium prevention have been formulated. Non-pharmacologic strategies are considered best and include:

- providing time, spatial, and situational orientation
- family involvement
- sensory aids such as glasses and hearing aids
- memory clues and cognitive stimulation
- early mobilization
- aiding sleep at night with noise and light reduction

Effectiveness of non-pharmacologic strategies was demonstrated by the Hospital Elder Life Program (HELP), in which hip fracture repair subjects had reduction in the occurrence of delirium from 50% in the usual care group to 32% in the intervention group. A recent meta-analysis of 14 studies of multi-component non-pharmacological interventions showed effectiveness in reducing delirium incidence and preventing falls, with a trend toward decreasing length of stay and avoiding institutionalization.

Pharmacologic prevention strategy includes:

- Minimize use of pharmacologic agents that may contribute or worsen delirium
- Judicious use of sedation
- Adequate treatment of pain

It is best to avoid all pharmacologic agents with high deliriogenic potential or anticholinergic load to the extent possible, and includes avoiding GABA-ergic agents to control agitation and for sedation except in cases of central nervous system-depressant withdrawal (i.e. alcohol, benzodiazepines, barbiturates) or when more appropriate agents have failed. Use of opioid agents for management of agitation should also be avoided and opioid-sparing strategies like parecoxib could help in preventing post-operative delirium.

A systematic review and meta-analysis revealed that use of dexmedetomidine for sedation was associated with less delirium compared to conventional GABA-ergic agents like midazolam or propofol. Indian Society of Critical Care Medicine's survey however revealed that nearly all respondents use midazolam for sedation (95%) followed by propofol (68%) and dexmedetomidine (60%).

REDUCE trial which evaluated delirium prevention with haloperidol did not show any benefit[10]. Meta-analysis on the use of statin therapy did not show any beneficial effects

either. However, perioperative use of prophylactic antipsychotics may reduce the overall risk of postoperative delirium and a meta-analysis of 38 studies supported dexmedetomidine sedation, multicomponent interventions and antipsychotics in preventing postoperative delirium[13]. Medications which strengthen circadian rhythm like suvorexant (potent orexin antagonist) and ramelteon (melatonin agonist) were associated with lower risk of delirium in the elderly[10] and results from large RCT on prophylactic melatonin (Pro-MEDIC trial) are awaited. Acetylcholinesterase inhibitors have protective role in patients with dementia.

Society of Critical Care Medicine has developed a group of interventions called the ABCDEF bundle, which incorporate various prevention strategies listed above and can help reduce delirium, improve pain management, and reduce long-term consequences for adult ICU patients [13]. It's A to F ingredients are:

- Assess, prevent and manage pain
- Spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT)
- Choice of sedation
- Delirium monitoring and management
- Early mobility and exercise
- Family engagement and empowerment

A recent meta-analysis that included 26384 patients from 11 studies failed to support efficacy of bundle interventions in reducing prevalence and duration of delirium, but supported effectiveness in reducing the proportion of patient-days with coma, hospital length of stay, and 28-day mortality [15].

4.4. C. Surveillance and accurate diagnosis

Surveillance is critical to timely detection of delirium, and use of standardized surveillance tool e.g. CAM, Intensive Care Delirium Screening Checklist (ICDSC), S-PTD and 4-AT and diagnostic tool like CAM-ICU or MDAS is helpful. Especially noteworthy is the under-recognition of hypoactive type. A multinational survey from 47 countries revealed that while delirium monitoring is carried out in 70% of the ICUs, only 42% used a validated screening tool [10].Indian Society of Critical Care Medicine's survey found that only 35% of the intensivists reported assessing for delirium.[16] Finding from these surveys underscores the need for training medical personnel at all levels regarding the prevalence and symptoms of delirium, its subsyndromal presentations and use of screening tools. Rapid Assessment Test for Delirium (4AT) and Stanford-Proxy Test for Delirium (S-PTD) are newer tools with 90% and 79% sensitivity and 84% and 90.8% specificity respectively. Other useful tools are the Richmond Agitation-Sedation Scale (RASS), the Sedation-Agitation Scale (SAS), and Neelon and Champagne (NEECHAM) Confusion Scale for nurses.

International Classification of Diseases (ICD-10) and DSM-5 are the diagnostic gold standards of delirium. Important points in clinical work-up of delirium include:

- History - present and past medical history, risk and precipitating factors, collateral history, medication history, drug and alcohol history, sudden onset (within hours or days) with a fluctuating course
- Physical Examination –careful note of vitals, oxygen saturation, examination of skin for "tracks"(I.V.drug use), any signs of infection, any source of pain
- Neurological examination - re-emergence of pathologic primitive signslikeGlabellar tap reflex, Rooting reflex, Snout reflex, Suck reflex, Grasp reflex, Palmomental reflex and Babinski sign
- Mental Status Examination (Core domains of delirium):

- Psychomotor dysregulation - Agitation (Floccillation or Carphologia), Retardation or Mixed presentation
- Cognitive deficits: Clouding of consciousness, Inattention: impaired ability to direct, sustain and shift both visual & auditory attention, Disorientation in time place person, Memory impairment,
- Language impairments, (Rambling, Incoherent, or illogical speech,
- Disordered thinking -delusional thinking, Abstract thinking and comprehension,
- Executive dysfunction,
- Altered perceptions (illusions and hallucinations).
- Circadian rhythm dysregulation : 'Sundowning' sleep–wake cycle disturbances with nocturnal worsening
- Emotional dysregulation: affective lability characterized by anxiety, perplexity, fear, sadness, irritability, apathy, anger, or euphoria etc.

- Investigations – various indicated hematologic, biochemical, electrophysiological and imaging tests are important to uncover the aetiology. (For details please refer IPS practice guidelines for delirium)

4.4. D. Management of psychiatric and behavioural manifestations of delirium

Pharmacologic treatment is effective for all types of delirium. Antipsychotics are useful in ways more than one: to manage abnormally elevated levels of dopamine, provide restoration of putative hippocampal functions (eg, short-term memory) and reversal of other regional brain disturbances (eg, agitation, psychosis, primitive reflexes), as well as to protect neurons against hypoxic stress and injury. [13]

A systematic review of 28 studies of treatment of delirium with antipsychotic agents concluded that

- about 75% of patients receiving short-term treatment with low-dose antipsychotics display clinical improvement
- treatment response rates seem quite consistent across different patient groups and treatment settings
- no major differences in response rates between clinical subtypes of delirium
- no significant differences in efficacy for haloperidol versus atypical agent
- The dose of antipsychotic may depend on the type of delirium being treated

In case of hyperactive delirium, moderate-dose haloperidol is still considered the treatment of choice subject to the patient's cardiac condition and absence of significant electrolyte abnormalities.[13] In a study conducted on patients with agitated delirium in the setting of advanced cancer, addition of lorazepam to haloperidol resulted in a significantly greater reduction in agitation at 8 hours; more data will help to assess generalizability and adverse effects of the combination.[17] When use of haloperidol is not desirable or contraindicated, atypical antipsychotics should be considered. More data exist for risperidone and quetiapine whereas data are limited for olanzapine, aripiprazole, lurasidone and paliperidone. Sedative potential and half life are important considerations in choosing any one of them. Clozapine and ziprasidone are best avoided.

It is safe practice before prescribing antipsychotic agents [13]:
(a) To obtain 12-lead electrocardiogram (ECG) and measure QTc
(b) To check electrolytes, and correction of potassium (K) and magnesium (Mg) if needed

(c) To review patient's medication list and identify any other agents with the propensity to prolong QTc, and if possible, avoid other medications known to increase QTc and/or inhibitors of CPY3A4
(d) Discontinue antipsychotic use if QTc increases to greater than 25% of baseline value or is greater than 500 msec

Evidence about the utility of other pharmacotherapeutic agents in management of delirium [13]

i. Acetylcholinesterase inhibitor (rivastigmine, donepezil) in patients of delirium superimposed on known cognitive deficits or a history of recurrent delirium. Initial data were promising but more recent studies have not been able to replicate findings. At least one study suggested an increased mortality associated with their use, warranting caution. Physostigmine has been suggested as first-line treatment for the management of the central anticholinergic syndrome and antimuscarinic delirium.

ii. Melatonin or melatonin agonist ramelteon is helpful to promote sleep in all types of delirium.

iii. Alpha-2 agonists like dexmedetomidine and clonidine have role in protection against neuronal injury and worsening of delirium associated with acute norepinephrine release secondary to hypoxia or ischemia. Primary sedative agents can be changed from GABA-ergic agents like propofol or midazolam to dexmedetomidine. Clonidine is also an alternative, especially to wean patients off dexmedetomidine.

v. Anticonvulsant and other agents with glutamate antagonism or calcium channel modulation - Valproic acid is increasingly used in the management of agitated delirious patients who are either not responsive or cannot tolerate conventional treatment, however there are limited data. Same is true of carbamazepine and gabapentin. Amantadine and memantine could be useful to minimize glutamate-induced neuronal injury particularly in cases of traumatic brain injury (TBI) and cerebrovascular accident (CVA).

Pharmacologic treatment of hypoactive delirium involves very-low dose haloperidol given just before sun down, or low dose of risperidone or aripiprazole. In case of extreme psychomotor retardation or catatonic features without psychosis, use of psychostimulants like modafinil, methylphenidate or dextroamphetamine may be considered. Amantadine, memantine, or bromocriptine may help in management of extreme psychomotor retardation, particularly in cases of TBI and CVA.
Non-pharmacologic treatment of all types of delirium is the same as non-pharmacologic strategies of prevention of delirium described in section B.

4.4. E. Identification of aetiology and treatment of underlying medical condition(s)

- The definitive treatment of delirium is the accurate identification and timely treatment of its underlying causes, which is entrusted to ICU consultee team of intensivist and physician/surgeon. Quick and safe correction of malnutrition, dehydration, and electrolyte abnormalities is part of general management and so also minimization of use of pharmacologic agents that may contribute or worsen delirium, whereas specific management is dependent upon the underlying cause(s). Acronym "I WATCH DEATH" iscommonly used as a checklist to investigate the underlying cause[18],[19] (table 4).

Table 4: Delirium aetiology acronym "I WATCH DEATH"

Infection	Systemic infections affecting brain, CNS infections
Withdrawal	Alcohol, Sedatives
Acute metabolic	Acid-base, electrolyte imbalance, kidney or liver failure
Trauma	Brain injury, Surgery, Severe burns, heat stroke, hypothermia
CNS pathology	Tumour, epileptic seizure, hydrocephalus, vasculitis, autoimmune encephalitis, meningeal carcinomatosis
Hypoxia	Respiratory failure, left heart failure, hypotension, anaemia, carbon monoxide poisoning
Deficiencies	Vitamin deficiency
Endocrinopathies	Cortisol or glucose dysregulation, hypothyroidism, hyperparathyroidism.
Acute vascular	Cerebrovascular accidents, shock, arrhythmias, hypertensive encephalopathy
Toxins/drugs	Pesticides, solvents, vitamin intoxication, alcohol & other illicit drugs
Heavy metals	Lead, manganese, mercury

*adapted from O. Joseph Bienvenu[19]

Additional points about management of delirium linked to alcohol withdrawal, a common condition in clinical practice, find mentioned in a later section.

5.0. Organic brain syndromes linked specifically to adverse reaction / toxicity of psychotropic medication viz.

Neuroleptic Malignant Syndrome (NMS), Serotonergic Syndrome (SS), and toxicity of mood stabilizer specifically Lithium overlaps with delirium. Though their occurrence is rare, these are potentially serious conditions and it is important that psychiatrists are aware for prompt recognition and early institution of management.

5.1. Neuroleptic malignant syndrome (NMS) [20][21]

Neuroleptic malignant syndrome (NMS) is a life-threatening emergency associated an adverse reaction to dopamine antagonists or to rapid withdrawal of dopaminergic medications characterized by distinctive clinical syndrome of altered mental state, muscle rigidity, fever, and autonomic dysregulation. It develops within hours or days after exposure to a causative drug. Presence of dehydration, physical exhaustion, exposure to heat, hyponatremia, iron deficiency, malnutrition, trauma, thyrotoxicosis, alcohol, psychoactive substances, and presence of a structural or functional brain disorder are the risk factors. Mortality rate is 5-20 % and average period of recovery is 7 to 11 days**.** IPS Clinical Practice Guidelines for management of Schizophrenia also touches upon factors associated with risk of NMS.[22]

Table 5: Medications associated with causation of NMS

Typical antipsychotics	Atypical antipsychotics	Nonneuroleptics with antidopaminergic activity	Dopaminergics (withdrawal)	Others

Haloperidol Fluphenazine Chlorpromazine Prochlorpromazine Trifluoperazine Thioridazine Thiothixene Loxaapine Perphenazine Bromperidol Clopenthixol Promazine	Clozapine Olanzapine Risperidone Quetiapine Ziprasidone Aripriprazole	Metoclopromide Tetrabenazine Reserpine Droperidol Promethazine Amoxapine Diatrizoate	Amantadine Toclapone	Lithium Phenalzine Dosulepine Desipramine Trimipramine

5.2. Diagnosis:

NMS should be suspected if the triad of fever, muscle rigidity, and altered sensorium is seen in patients exposed to antipsychotics. Diagnosis is based on clinical features of severe muscle rigidity & extrapyramidal symptoms including opisthotonos, trismus, blepharospasm, and oculogyric crisis, and hyperpyrexia along with two or more of – diaphoresis, dysphasia, tremor, incontinence, changes in level of consciousness ranging from confusion to coma, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, laboratory evidence of muscle injury (eg, elevated CPK- 10 fold rise). The symptoms are not due to another substance or a neurological or other general medical condition, nor due to other mental disorder.

5.3. Laboratory findings:

- Leukocytosis (counts up to 40,000 per cmm)
- Elevated CPK
- Mild elevations of lactate dehydrogenase, alkaline phosphatase, and liver transaminases
- Iron deficiency (a low serum iron concentration)
- Electrolyte abnormalities like hypocalcaemia, hypomagnesaemia, hypo- and hypernatraemia, hyperkalemia and metabolic acidosis
- CSF studies usually normal
- EEG – Non generalized slowing

5.4. NMS is to be differentiated from:

- Infections: Meningitis or encephalitis, brain abscess, sepsis, rabies
- Metabolic illnesses :Acute renal failure, rhabdomyolysis, thyrotoxicosis, pheochromocytoma

- Environmental: Heat stroke, spider envenomations

- Drug-induced: Malignant hyperthermia, neuroleptic induced syndromes - Parkinsonism, acute dystonia, acute akathisia, Tardive dyskinesia, postural tremor. Non-neuroleptics induced syndromes - serotonin syndrome, anticholinergic delirium, MAO inhibitor toxicity, lithium toxicity, salicylate poisoning, strychnine poisoning. Drugs of abuse - cocaine, amphetamine, methamphetamine, MDMA, phencyclidine.

- Serotonin syndrome: Use of selective serotonin reuptake inhibitors

- Drug-withdrawal syndrome: Alcohol, benzodiazepine, baclofene, sedatives, hypnotics
- Neurological or psychiatric disorder: Parkinsonism, nonconvulsive status epilepticus, lethal or malignant catatonia
- Autoimmune: Polymyositis

5.5. Management of NMS:

Being a rare complication management is base on case series and includes

- Stop all dopamine blockers
- Start dopamine agonist medicines if NMS is caused by stopping it

5.5.1. Supportive care

- Adequate hydration, correction of electrolyte imbalance, external cooling (ice packs in axilla, cooling blankets), gastric lavage of ice water and use of paracetamol.
- Lorazepam is used for agitation and clonidine may be used for autonomic instability (hypertension).
- Preventive measures for deep vein thrombosis.

5.5.2. Specific measures:

- **Bromocriptine**, starting with 2.5 mg 2 or 3 times daily. Increase doses by 2.5 mg every 24 hours until a response or until reaching a maximum dose of 45 mg/day, for reversing hypodopaminergic state. Maintained up to 10 days for oral antipsychotics and 2 to 3 weeks for depot preparations.
- Other drugs like amantadine hydrochloride, levodopa, apomorphine, dantrolene can also be tried.
- ECT has controversial reports, still recommended where nonpharmacological treatment is required or where drug treatment fails

5.6. Restarting Antipsychotics:

- Since recurrence may happen after restarting high potency antipsychotic or early after recovery, wait for at least 2 weeks for oral antipsychotics or 6 weeks for depot antipsychotics, prefer low potency antipsychotics starting with low dose and up-titrate slowly & carefully.

6.0. Serotonin syndrome [23], [24], [25], [26]:

Serotonin syndrome (serotonin toxicity) is a potentially life threatening drug induced syndrome due to increased concentration of serotonin in central nervous system, resulting from either therapeutic drug use, intentional self overdosing or an inadvertent interaction between drugs. Selective serotonin reuptake inhibitors (SSRIs) are amongst the commonest groups of drugs taken in overdose, and serotonin toxicity

occurs in 15% of SSRI overdoses. Severe serotonin toxicity is a medical emergency complicated by hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, and adult respiratory distress syndrome.

Table 6: Medications associated with causation of Serotonin Syndrome

Drug	Drug combinations
MAOIs	MAOIs alone MAOIs with SSRIs or SNRIs or TCAs or Opiates Paroxetine or Clomipramine with Methylene blue Phenelzine with meperidine Tranylcypromine and imipramine
SSRIs	SSRIs alone SSRIs with MAOIs or SNRIs orTCAs or Opiates or Ttriptans Fluoxetine with carbamazepine or Phentermine or fentanyl
SNRIs	SNRIs with MAOIs or TCAs or opiates or Triptans Venlafaxine alone Venlafaxine with lithium or Calcineurin inhibitors Venlafaxine with mirtazapine and Tramadol Venlafaxine with Amitryptiline and meperidine Venlafaxine with mirtazapine or Tranylcypromine Venlafaxine with methadone and Fluoxetine Venlafaxine with methadone and Sertraline Venlafaxine with tramadol and trazadone and Quetiapine Buspirone with SSRIs Mirtazapine alone Mirtazapine with SSRIs Trazodone with Amitryptiline and lithiumOpiates with MAOIs or
Other Antidepressants	SSRIs or SNRIs or Ttriptans
Opiates	Tramadol alone Tramadol with mirtazapine and Olanzapine
Over-the-Counter Cold Remedies	Dextromethorphan with SSRIs or Amitryptiline or chlorpheniramine Dextromethorphan with risperidone and Amitryptiline
Atypical Antipsychotics	Olanzapine with Lithium and Citalopram Risperidone with Fluoxetine or Paroxetine.
Antibiotics	Ciprofloxacin with venlafaxine and methadone Fluconazole with citalopram Linezolid with SSRIs or Tapentadol
Serotonin releasing agents	Fenfluramine, Sibutramine, Amphetamine, methamphetamine, methylphenidate, phentermine, Synthetic stimulants—Ecstasy, bath salts (cathinones, phenylethylamines)

*Adapted from Jacqueline Volpi-Abadie, et al.[18]

6.1. Diagnosis:

Serotonin syndrome should be suspected if the triad ofneuromuscular excitation, autonomic nervous system excitation and altered mental state is seen in patient is exposed to a

serotonergic drug. Many researchers groups viz. Sternbach, Hunter, Radomski and colleagues, and Dounkeley have proposed diagnostic criteria.

- Diagnosis in **mild** cases is based on tachycardia, mild hypertension, mydriasis, diaphoresis, shivering, tremor, myoclonus and hyperreflexia without fever.
- In **moderate** cases, hyperthermia (40.8C), hyperactive bowel sounds, horizontal ocular clonus, mild agitation, hypervigilance, and pressured speech is seen.
- In **severe** cases, hyperthermia greater than 41.18C, dramatic swings in pulse rate and blood pressure (autonomic dysfunction), delirium, and muscle rigidity.
- Some patients develop **complications** like seizures, rhabdomyolysis, myoglobinuria, metabolic acidosis, renal failure, acute respiratory distress syndrome, respiratory failure; diffuse intravascular clotting, coma, and death. Onset is acute <12 to 24 hours with rapid progression. Resolution can be expected within 24 hours if uncomplicated, and mortality low (<1%) when proper treatment is given.

6.2. Laboratory Investigations:

There is no specific laboratory test for diagnosing serotonin syndrome. However raised total creatine kinase, leukocyte count and transaminase levels and lower bicarbonate levels may be seen. [5]

6.3. Serotonin Syndrome is to be differentiated from

- Malignant neuroleptic syndrome
- Infectious causes
- Herpetic encephalopathy
- Heat stroke
- Myocardial necrosis
- Delirium tremens
- Intoxication by adrenergic or anticholinergic agents

6.4. Management of Serotonin syndrome:

Treatment is mainly supportive. All serotonergic medication is to be stopped first.

6.4.1. Supportive care

- Adequate hydration, correction of electrolyte imbalance, external cooling (ice packs in axilla, cooling blankets), and prescription of benzodiazepine for agitation.
- In case of severe agitation and hyperthermia 5HT-antagonist (cyproheptadine) withan initial dose of 12 mg, with the addition of 2 mg every 2 hours if symptoms persist, may be used.
- Severe hypertension/tachycardia can be managed with esmolol or nitroprusside.
- In severe cases chlorpromazine IM injection withan initial dosage of 50 to100 mg is used, and physical restraints avoided as it may contribute to mortality by enforcing isometric muscle contractions that are associated with severe lactic acidosis and hyperthermia.

- However, it is advisable to avoid both Bromocriptine and chlorpromazine if diagnosis is uncertain, and NMS is a possibility.
- Sedation and paralysis with a non depolarizing agent and intubation/ventilation may be warranted in severe cases.

7.0. Lithium Toxicity [27]:

Lithium, the drug of choice for bipolar disorder, has a narrow therapeutic index and excessive intake or impaired excretion can result in its accumulation and toxicity. It finds mention in the IPS Clinical Practice Guidelines for Management of Bipolar Disorder.[28] Early identification is important since ignoring lithium toxicity can have serious consequences and can lead to coma, brain damage, or even death. Moderate or severe toxicity warrants ICU management.

Excessive intake could result from dose modifications for patients on long-term lithium treatment or accidental ingestion /suicidal intent of excessive amount of lithium tablets. Impairment of excretion of lithium can be caused by several factors like Sodium and volume depletion because of conditions like vomiting, diarrhoea, febrile illness, renal insufficiency, excessive exercise, water restriction, excessive sweating, low sodium diet, and congestive heart failure. Drugs reducing glomerular filtration rate may also cause chronic toxicity. 95% of lithium excretion takes place through kidneys and renal clearance of lithium is usually 10 to 40 mL/ minute. Nephrogenic diabetes insipidus, which can be precipitated by long-term lithium treatment, leads to diminished urinary concentrating capacity of the kidneys and may lead to toxicity. Elder patient are vulnerable since lithium clearance may be decreased and half-life prolonged.

7.1. Lithium toxicity usually classified into three major categories:
- Acute overdose in a lithium-naive patient.
- Acute overdose in a patient on chronic therapy (acute-on-chronic).
- Chronic over-medication or drug accumulation (associated with the most serious toxicity).

7.2. The severity of toxicity is divided into mild, moderate, and severe grades.
- **Mild toxicity**: nausea, vomiting, lethargy, tremor, and fatigue (Serum lithium concentration between 1.5-2.5 mEq/L).
- **Moderate toxicity:** confusion, agitation, delirium, tachycardia, and hypertonia (serum concentration between 2.5-3.5 mEq/L.
- **Severe toxicity**: Coma, seizures, hyperthermia, and hypotension (serum concentration >3.5 mEq/L.

7.3. Assessment
- Determination of ingested amount, time of ingestion, whether there are co-ingestants, and if the ingestion was intentional or unintentional is important. It is noteworthy that lithium toxicity signs may not conform to the measured lithium level.

- Lithium toxicity is to be differentiated from - acute hypoglycaemia, alcohol toxicity, anticholinergic toxicity, delirium, heavy metal toxicity, neuroleptic agent toxicity, stroke, etc.

- Assessment should include cardiac monitoring, oxygenation and monitoring of urine output, serum electrolytes, calcium, renal function, glucose, serum lithium level, and thyroid-stimulating hormone.

7.4. Treatment principles:

- **Decontamination** – charcoal should be administered if co-ingestants are unknown. Gastric lavage is useful particularly in the case of regular-release preparations and patients presenting early to the emergency department. Whole-bowel irrigation should be considered in case of sustained-release preparations, or massive ingestion of regular-release products.

- **Elimination -** The most appropriate method of lithium removal is haemodialysis, particularly if patient demonstrates signs and symptoms of severe lithium poisoning or is having a renal failure.

- **Disposition -** All patients with features of toxicity, even those with normal serum lithium levels, should be admitted for monitoring in the hospital and those with moderate or severe symptoms in intensive care unit. Serial lithium serum level should be obtained every 6 hours in case of asymptomatic patients after an acute ingestion. This should be continued until descending drift is observed and patients should not be discharged until they are asymptomatic and serum lithium level falls to below 1.5 mEq/L.

8.0. Psychosis in the ICU [29],[30],[31]

Historically 'Intensive Care Unit Psychosis', 'Intensive Care syndrome', 'postcardiotomy delirium after heart surgery', 'cardiac psychosis', 'ICU Syndrome' were some terms used synonymously with Delirium.[20]

Almost any medical condition that affects brain can cause an organic psychosis. Another group of patients in ICU for whom psychiatry referral may be made are cases of pre-existing functional psychosis who have developed some medical complications.

Some common types of organic psychosis are:

- Delirium with psychotic features: commonest organic psychosis, discussed in detail in previous section.

- Psychosis associated with dementia is also common.

- Other disorders associated with psychosis include Parkinson's disease, HIV, head trauma, and Huntington's disease.

8.1. Psychosis associated with dementia[30]:

- Other causes presenting with features of dementia e.g. Immune disorders (Lupus) endocrine disorders (hypothyroidism, hypercalcemia and hypoglycaemia) or vitamin deficiency (Thiamine, Niacin) or an untreated infection should be ruled out.

- Treatment of psychosis in patients with dementia is challenging. There is a black box warning against antipsychotics due to 1.6 to 1.7 fold increased risk of mortality. Use of risperidone and Olanzapine may be justified in some cases of persistent severe aggression and/or psychosis in cases of Alzheimer's. Polypharmacy should be avoided to minimise drug -drug interactions in elderly patients and there should be regular review; effect is modest at best.

8.2. Psychosis in Parkinson's disease (PD) [30]:

- Non-motor symptoms like hallucinations and delusions can be present in P.D. Patients with PD often have hallucinations in which they have insight. Dopaminergic medicines improve motor symptoms but exacerbate psychosis symptoms. The risk of development of psychosis & other psychiatric symptoms is increases by 75 % when dementia is associated with PD.

- **Treatment:** Common antipsychotics may improve psychotic symptoms but may worsen motor symptoms, and are not a suitable choice. **Pimavanserin** is a novel antipsychotic agent, which is serotonin inverse agonist with low binding affinity to dopamine receptors. It has shown a better safety and efficacy profile in psychosis associated with PD, doses needed to be adjusted as per the co-morbidities and renal and hepatic dysfunction. The usual dose is 34 mg PO /day in bid doses.

8. 3. Malignant Catatonia [31]:

Malignant Catatonia is the severe form of catatonia that may need admission in ICU. The management is similar to that of NMS. ECTs may have beneficial effect.

8.4. Status epilepticus in the ICU:

Complex partial seizure status or myoclonic status epilepticus may present like psychiatric syndromes, and needs to be differentiated and treated according to seizure type with specific AEDs as per the guidelines.

9.0. Patient with suicidal attempt in the ICU [32], [33], [34]:

- Suicide attempt is self-injurious behaviour with a nonfatal outcome with evidence that the person intended to die.

- About one third of ICU admissions are patients attempting suicide. Studies have shown that over 50%-95% of theses have history of psychiatric disorder or prior treatment.

9.1. Management of suicide attempt is considered in 2 parts:

A.9.1. Management of patient with attempted suicide

B.9.1. Considering strategies for prevention of further suicidal attempts

A. 9.1. Psychiatric Management of survived patient after attempted suicide

- Psychiatrist should establish rapport and therapeutic alliance and should approach the patient in a non-judgmental manner initially asking open ended questions. The interview could be semi-structured.
- Focus should be on present suicidality, specific psychosocial situation, past and family history of suicide, individual's strengths and vulnerabilities and modifiable risk factors. Also assess past history of psychiatric illness and treatment history, previous suicidal attempts and substance abuse.[32]
- Conduct thorough psychiatric evaluation to establish psychiatric diagnosis, suicidal ideation and plan, and also assess degree of suicidality to avoid further attempts.
- Focus on following specific factors or symptoms which increase risk of suicide:
    - i. Anxiety ii. Hopelessness iii. Command hallucinations iv.Impulsivity and aggression v. Alcohol intoxication vi. Past suicide attempts vii. History of childhood physical/sexual abuse viii. History of domestic partner violence ix. Past history of treatment/hospitalization x. Presence of physical illness xi. Family history of suicide. xii. Recent or concurrent life stressors. Xiii.The person's current living situation and social supports.
- Patient's safety is of utmost importance; Safety measures could be:
    - Keep the patient in an area that can be easily observed, which is safe but non-restrictive and having no fixtures which may be used for attempting hanging.
    - Light/electricity fixtures should be concealed one.
    - One-to-one continuous observation; wherever possible 24-hour attendance by near relatives and friends to encourage safety and social support.
    - Medication should be in the custody of ICU staff who will administer as per orders.
    - Removal of the patient's access to lethal weapons, especially guns, sharp objects, duptta, saree etc. Provide hospital cloths.
    - Prepare a safety checklist and share it with staff & accompanying person/observer.

- Treatment plan: It should be done in collaboration with consultee and it is divided into pharmacologic & nonpharmacologic interventions.

9.2.1. Pharmacologic interventions:

- **Antidepressants :**

- TCAs should be avoided in patients with suicidal ideation as overdose can prove lethal.
- SSRIs and SNRIs if used should honour FDA black box warning and alternatives suggested may be followed, particularly in young adolescent patients with agitated depression since they can increase suicidal ideation and plans temporarily in early phase of treatment.
- Bupropion, Mirtazapine can be alternatives used for depression, both bipolar & unipolar in this group.
- One study found Paroxetine to be more effective than Bupropion
- **Anxiolytics :**
- Anxiolytics may be used in the initial phase to take care of anxiety symptoms either alone or along with other psychotropic medication.
- **Antipsychotics:**
- In patients of schizophrenic with suicidal ideation, atypical antipsychotics such as clozapine, risperidone, olanzapine and ziprasidone have been shown to be effective in reducing positive symptoms and also negative symptoms to lesser extent. Mortality rate can be potentially decreased by about 85 percent using Clozapine in suicidal schizophrenic patients. In recent studies, addition of aripriprazole to antidepressants in cases of inadequate response showed reduction in depressive symptoms and suicidal ideation.
- **Mood stabilizers:**
- Lithium is only mood stabilizer which in addition to stabilization of mood also reduces suicidal ideation.
- Carbamazepine, oxcarbazepine, Felbamate, gabapentin, Lamotrigine, levetiracetam, pregabalin, tiagabine, topiramate, valproate &zonisamide are not as such effective in reducing suicidality in patients with epileptic psychosis.
- Varenicline, associated with black box warning should be avoided.
- Recently Ketamine infusion 0.5 mg/kg is proved to have rapid antidepressant and antsuicidal effect, and can be tried in acute situations.
- Overall, lithium & clozapine have been shown to be effective in reducing suicidality**.**

9.2.2. Physical therapy:

- Electroconvulsive therapy: ECTs are effective in reducing suicidality in acute situations. A full trial can be given.

9.2.3. Psychotherapy: CBT (Cognitive behaviour therapy), DBT (Dialectical Behaviour Therapy) and IPT (Interpersonal Psychotherapy) in combination with medical therapies have positive effect on managing suicidality.

9.2.4. Documentation of assessment and management plan should be meticulous and carefully done. Management plan should be informed to patient.

B. 9.3. Considering strategies for prevention of further suicidal attempts:

- Psychiatric diagnosis may be revealed for the first time after ICU admission on account of suicidal attempt.
- Studies found that the rate of death in re-attempters ranges from 2.3% to 4% in index attempt survivors ,In another study at follow-up, 37.6% of the participants had died (all causes), of which 7.2% died by suicide and 53% of these within 5 years of the index suicide attempt. Considering this risk, strategy to prevent further suicidal attempts should be followed as follows.

9.3.1. Assessment:

- Details of psychiatric and medical illness, past attempt(s), and family history of suicide are important. Establish clinical diagnosis. Assess risk factors given in table 7, focus on modifiable factors**.**

Table 7: Risk factors for suicide

Adolescence and old age	Lethality of previous attempt
Identity as a bisexual or homosexual	Living alone
Criminal behaviour	Low self-esteem
Cultural sanction for suicide	Male sex
Delusions	Physical illness or impairment
Disposition of personal property	Previous serious attempts
Divorced, separated, or single marital status	Protestant or nonreligious status
	Recent childbirth
Early loss or separation from parents	Recent loss
Family history of suicide	Repression as a defence
Hallucinations –command type	Secondary gain
Homicide	Severe family pathology
Hopelessness	Severe psychiatric illness
Hypochondriasis	Sexual abuse
Impulsivity	Signals of intent to die
Increasing agitation	Unemployment
Increasing stress	
Insomnia	

- Evaluate for patient's strengths & vulnerabilities-Table 8.

Table 8: Protective factors

• Positive Problem-solving skills • Self confidence • Possesses healthy and well-developed social skills • Has family & children • Has family & social support • Positive integration into society • Belief in religion • Maintaining positive values and spirituality • Respects cultural & traditional values • Adequate treatment for mental/physical illnesses

- Inquiry into presence or absence of suicidal intent or thoughts, suicidal plans or behaviours must be made in detail. Assess the severity of intent and potential lethality of the plan. Various tools are available for this purpose. Assess whether the intent is persistent and active, suicidal communication is verbalized and suicidal behaviour is obvious with self injurious behaviour or previous attempt.

9.3.2. Warning signs:

- Oral expression about suicidal thought
- Expressing plans for suicide
- Expressing hopelessness about the future
- Displaying severe/overwhelming emotional pain or distress
- Loneliness feeling
- Helplessness
- Believing to be a burden to others
- Making arrangements for property management (e.g. making will)
- Showing worrisome behaviors
- Marked change in behaviour, mainly in the presence of other warning signs, including:
    - Withdrawal from social situations/connections
    - A recent feeling of agitation or irritability
    - Out-of-character anger or hostility

- Sleep changes

9.4. Scales for suicidal ideation:

- The Beck Scale for Suicide Ideation (SSI)
- Beck Hopelessness Scale (BHS)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Management plan is the same as described in previous section.

10.0. Drug overdose, intoxications & withdrawal states in ICU[27],[35],[36],[37],[38]:

10.1. Drug overdose:

Drug overdose is ingestion or application of a drug or other substances in quantities greater than recommended or typically practiced, which may result in toxic state or even death. Patients after intentional or accidental overdose are often treated in ICU and psychiatric consultation is sought.

Drug toxicity should be considered when a patient acutely develops symptoms like vomiting, diarrhoea, seizures, respiratory distress, symptoms of metabolic acidosis, symptoms suggesting multisystem disorder, shock or coma. Any change in the behaviour, cognition or autonomic function should suggest either withdrawal or new toxic process due to medications used. Similarly, any subsequent shifts in patterns of autonomic indices and behaviour during the hospital course should open the possibility of a new toxic process mediated by either the treatment or withdrawal from discontinued substances.

The clinician should review history and all previous records, note history of previous toxicity or withdrawals and perform thorough physical examination. In case of doubt, drug screen should be performed. Strongest predictors for needing ICU treatment are respiratory insufficiency, age > 55, and a Glasgow coma scale < 6. The consultee & the liaison psychiatrist should decide

- Whether the psychotropic medication or other medications should be stopped which are not essential (drug wash-out) except those which can cause withdrawal symptoms.
- Change of previous medicine can be considered e.g. safer drugs may be considered in place of TCAs or MAOIs after patient's condition has stabilized.

Table 9: Drug toxicity of some common medicines

Class	Examples of drugs	Action	Antidote	Dose
Sedatives & hypnotics	Benzodiazepines Non-benzodiazepine GABA agonists Barbiturates Ethanol Chloral hydrate	CNS depression, slow respiration, hypothermia,	Flumazenil.	IV:0.5 mg over 30 s in adults, Consider lower doses in

		hypotension, hyporeflexia and bradycardia (mild)		children; may use 0.005–0.01 mg/kg at 0.2 mg/min rate in children; may repeat q30–60 min prn[36]
Antipsychotics	Chlorpromazine Promethazine Prochlorperazine Fluphenazine Perphenazine, Haloperidol Olanzapine Quetiapine	Hypotension, Arrhythmias, Oculogyric crisis, trismus, dystonia, ataxia, parkinsonism, neuroleptic malignant syndrome anticholinergic manifestations	Bromocriptine Dantrolene: for NMS	PO: 5 mg q12h increasing to effect, as high as 10 mg q6h. IV 3–10 mg/kg over 15 min with oral doses of 25–600 mg/d to maintain response[36]
Serotonergics.	Tricyclic Antidepressants, MAO inhibitors Buspirone	Akathisia Tremor agitation, hyperthermia hypertension hiaphoresis hyperreflexia clonus, lower extremity muscular hypertonicity diarrhoea	Cyproheptadine 4mg or 2mg/5ml syrup	12 mg initial dose followed by 2 mg every 2 hours till clinical response
Sympathomimetic psychostimulants	Amphetamines Pseudoephedrine Phenylephrine Ephedrine Cocaine	Hypertension tachycardia arrhythmias agitation paranoia hallucinations mydriasis nausea vomiting abdominal pain	No specific antidote	Treatment symptomatic with- Sodium bicarbonate, hydralazine, nitroprusside, or phentolamine, -for severe hypertension Haloperidol

		piloerection		for agitation
Anticholinergics	Atropine, Antihistamines Scopolamine AntispasmodicTricyclic Antidepressant PhenothiazinesAntiparkinsonian agents Jimson weed Psychedelic mushrooms	Agitation, Hallucinations, Abnormal Movements (Eg, Carphology), Tachycardia, Mydriasis, Dry Membranes, Hyperthermia, Decreased Bowel Sounds, Urinary Retention, Flushed/Dry Skin	Physostigmine Sodium bicarbonate (For TCAs)	0.05 mg/kg IV at a rate not to exceed 0.5 mg/min, with doses no more frequent than hourly[36] IV: 50 mEq per dose to address acidemia and/or ECG signs of sodium channel blockade. For an isotonic solution to continue alkaline fluid resuscitation, mix 150 mEq NaHCO3 (typically 3 ampoules) and 40 mEqKCl in dextrose. Goal serum pH 7.5–7.55.[36]
Opioids	Oxycodone, Hydrocodone Hydromorphone Fentanyl Morphine Propoxyphene Codeine Heroin	CNS depression respiratory compromise miosis bradycardia hypotension, hypothermia pulmonary edema hyporeflexia seizures	Naloxone	IV: Start 0.05 mg with repeat dosing every 15 s to reversal of respiratory depression and/or unconsciousness; once achieved, repeat the same total dose q1h prn. Higher

				doses (1–2 mg or more) may be useful in a2-adrenergic agonist toxicity[36]
Cholinergics	Organophosphates Carbamate insecticides Cholinesterase inhibitors	'SLUDGE' **S**ialorrhrea **S**weating **L**acrimation, **U**rinary/Fecal incontinence, **G**astrointestinal cramping, **E**mesis bradycardia miosis pulmonary **e**dema weakness, paralysis muscle fasciculations	Atropine Pralidoxime (2-PAM)	IV: 1–2 mg doubled every 3–5 min until bronchorrhea resolves in adults; 0.03 mg/kg in children, similar titration. IV: 1–2 g over 30 min, then up to 500 mg/h in adults; 25–50 mg/kg over 30–60 min, then 10–20 mg/kg per h in children.[36]

10.2.1. Intoxication:

ICD-10 defines acute intoxication as a transient condition following the administration of alcohol or other psycho active substance resulting in disturbances in level of consciousness, cognition, perception, affect or behaviour, or other psychophysiological functions and responses. Intoxication is associated with high blood levels of alcohol or the drug.

Table 10: Alcohol and cannabis intoxication

Disorder	Onset	Clinical features	Differential diagnosis	Management
Alcohol intoxication	from 1 hour to 24 hours	Smell of alcohol in breath, slurred speech, incoordination, unsteady gait ,flushed face, nystagmus, irritability, loquacity, mood changes, later	Head injury, hypoglycaemia, postictal states, hepatic encephalopathy, meningitis, encephalitis, and	Symptomatic maintain circulation, respiration, blood pressure. Provide protective

		coma, death	intoxication with other psychoactive substances	environment, correct hydration, Haemodialysis in severe case
Cannabis intoxication /toxicity		Impaired attention, concentration, short-term memory and executive functioning. Nausea, postural hypotension, delirium, panic attacks, anxiety, myoclonic jerking, and psychosis in more severe cases	Hypoglycaemia, Electrolyte imbalance, CNS infections, Traumatic brain injury and intoxication with other psychoactive substances	Supportive care

10.3. Withdrawal states:

Table 11: Alcohol withdrawal- Delirium Tremens[38]

Disorder	Onset after cessation	Clinical features	Differential diagnosis	Management
Delirium Tremens (DT)	Onset within 48-72 hours, peak 4 to 5 days, may last for weeks	Delirium, autonomic instability, delusions, hallucinations, agitated behaviour, coarse tremors , 50 % patients having seizures may have DT	Delirium due to other causes Dementia Psychosis	Benzodiazepines-Lorazepam, Diazepam, Chlordiazepoxide Haloperidol Front loading eg. With diazepam achieve light sedation with5mg I.V.(repeat after10 minutes) Then 10 mg I.V.(Repeat after 10 minutes),Then 2o mg IV after 10 minutes then % to 20 mg IV per hour till light sedation or CIWR-Ar score <8 achieved. Symptom triggered:With diazepam 10–20 mg IV every 1–4 h repeat doses till CIWA-Ar score <8With lorazepam: 4 mg IV to be

				repeated every 10 min till either of the aims of front loading is achieved If severe delirium still persists even after 16 mg IV then 8 mg IV bolus is to be Administered[38]

11.0 Anxiety disorders in ICU [39],[40].[41]

- Anxiety in ICU patients is generally secondary to
    - The ICU setting
    - The patient's medical illness, or
    - The medications
- Anxiety can be caused by medical conditions including hypoglycaemia, hypoxia and an evolving myocardial infarction (MI). Patients may develop anxiety on account of the medicines they are receiving e.g. medicines such as theophylline for concomitant pulmonary disease, isoproterenol for cardiac rhythm disturbances, etc.
- Mechanical ventilation causes anxiety in patients who find it difficult to wean from ventilation.
- Anxiety may be a manifestation of alcohol, sedative, opiate, nicotine, or antidepressant withdrawal. Nicotine dependence is perhaps the most common withdrawal syndrome encountered in the ICU in patients with cardiovascular disorders.
- Fear of death or fear of disability, misconceptions about the illness and concern about prognosis, misinterpretation of display and alarms from the monitors in the ICU, and restriction of usual activities may all contribute to causation of anxiety in ICU. Illness and hospitalization may affect patient's ability to handle ongoing real life problems and may cause anxiety.
- Symptoms of panic disorder and other anxiety disorders overlap with symptoms of cardio- respiratory disease and patients may have pre-existing anxiety disorder too.
- Post-traumatic stress disorder (PTSD) is common during or after an ICU admission. Factors contributing to PTSD are
    - Prior psychopathology
    - Greater benzodiazepine administration
    - Post-ICU memories of frightening or psychotic experiences during admission.

11.1. Management of anxiety disorders in ICU

11.1. 1.Pharmacotherapy:

- Lorazepam is preferred over other benzodiazepines, and dose is adjusted to the minimum effective dose.
- As pain & anxiety are associated, effective pain management should be done

11.1.2. Non pharmacological therapies:

- Provide accurate medical information
- Have a supportive accompanying family member

- Explain the roles and meaning of the monitoring equipment
- Providing emotional support and reassurance, and
- Helping patient to accept the situation as denial can interfere with treatment.
- Use of relaxation technique
- Brief psychotherapies, including
    - Psychoeducation
    - Crisis intervention
    - Short-term psychotherapy
    - Supportive psychotherapy
    - Cognitive behavioral therapy
    - Hypnosis

12.0. Depression in ICU [42]:

- About 17% of patients admitted in ICU have history of taking SSRIs or SNRIs, and about 28% of ICU survivors report clinically significant depressive symptoms
- Symptoms of depression in ICU may result from:
    - Acute illness may directly cause depressive symptoms.
    - Acute illness can produce symptoms that mimic some aspects of depression.
    - Emotional reaction to patient to acute illness.
    - Secondary to medications.
    - The patient may have an independent major depressive disorder.

12.1. Diagnosis

- In the ICU setting it is preferable to err on the side of sensitivity in diagnosing depression as it outweighs the risk of missing potential depression.
- The PHQ-2 has a sensitivity of 87.8%, specificity of 71.6%, positive predictive value of 30.3%, and negative predictive value of 97.8% using 3 as the cut-off score.
- ICD-10/DSM V criteria are the gold standard of diagnosis.
- IPS guidelines for management of depression in special situations can be referred to.[42]

12.2. Treatment:

- In most patients illness is time-limited and does not require aggressive pharmacotherapy. In ICUs, antidepressants use is often limited.
- Patients requiring prolonged stays may develop an adjustment disorder with a depressed mood. It may respond to the initiation efforts for rehabilitation or psychotherapy.
- Stop offending drugs which may be responsible for major depressive disorder. (List provided in IPS guidelines for depression & depression in elderly people)
- In critically ill patients, hold antidepressants and when they become stable, antidepressants can be restarted.
- The SSRIs are drug of choice in case of established diagnosis on account of effectiveness, better safety profile & minimum drug-drug interactions.

- Care should be taken when patients are receiving other medications like Phenytoin sodium, Digoxin or Warfarin (monitor blood levels of these drugs as they have low therapeutic index, when one starts SSRIs.)
- Sertraline Escitalopram and citalopram have minimal chances of drug- drug interaction.
- Caution need to be exercise with Venlafaxine & Desvenlafaxine, which may cause an increase in mean blood pressure even at therapeutic dosages, and Buproprion which may lower the seizure threshold and has dopaminergic action.

13.0. Ethical issues:

- ICU care has come to be associated with high-tech, aggressive and often risk-filled medical care and ICU team is often confronted with ethical dilemmas, some of which are by-products of advanced technologies and therapies.

- Common ethical issues in ICU involve informed consent, application of restraint, decisions regarding life-sustaining treatments like CPR, withholding or withdrawal of life support, breaking bad news and organ donation, etc.

- **Informed consent**: one of the most important ethical issues and psychiatrist help may be sought for ascertainment of patient's capacity to consent. A related issue pertains to ascertainment of fitness for undergoing surgery, either in the context of pre-existing psychiatric disorder or new onset clouding of consciousness or any other psychopathology, and even emotionally challenging situation like amputation.

- **Restraints [43],[44]:** restraints, whether physical or chemical, limit both movement and autonomy and advocated only when no better option exists, and employed with caution.

- As per MHCA 17 section 97.1(a), states that it is the only means to imminent & immediate harm to the person concerned or to others. Restraints can be used for minimum duration, under one to one supervision of trained staff on the advice of a psychiatrist. It should safe; age and gender appropriate and also suitable to size and physical/ medical condition of the patient. One should monitor closely for any deterioration.

- In ICU set up, mittens, wrist and leg belts or waist belts can be used to avoid removing life support tubes and other aids, and also not allowing the patient get out of bed.

- If necessary chemical restraint using optimal doses of recommended medications just to have control undesirable behaviour.

- Physical restraints can only be used in severe cases.

- **End-of-life care:** Decisions about treatment at the end of life are often difficult /complex and psychiatrist may be called for helping the patient's family and

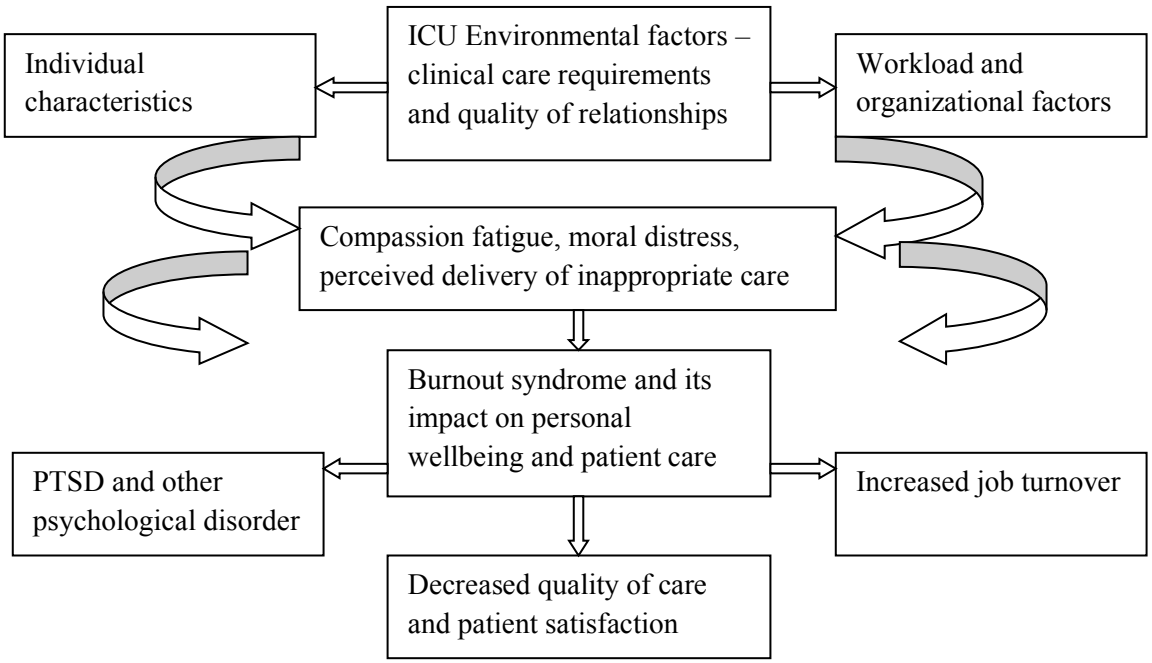
physician. The psychiatrist should consider relevant medical, ethical, and legal issues and decisions are best made after careful discussion with patient or surrogate.

- **Managing anticipatory grief:** The psychiatrist can also be called to help in breaking the bad news or to facilitate organ donation - both involving dealing essentially with anticipatory grief.

14.0. Stress and burn-out in ICU team [45]

- The impact that ICU's unique environment can have on healthcare professionals is receiving increasing attention. Exposure to high patient mortality, difficult daily workload and ethical challenges all contribute to excessive stress and resultant burnout. In 2016 Critical Care Societies Collaborative of USA took cognizance of the ICU professional's burnout and issued "Call for Action" Statement.

Factors associated with burnout (Figure 4) adapted from Kerlin et al[36]



- Burnout includes symptoms of emotional exhaustion, depersonalization, and a reduced sense of personal accomplishment. Two large national surveys (French and USA) revealed high level of burnout in critical care physicians – 46.5% and 44% respectively, and while several factors are contributory (figure 4), risk is higher in women physicians.
- Burnout not only impacts adversely personal health and wellbeing of ICU professionals but also has major adverse consequence for patient care, and therefore needs due attention.
- **Burnout mitigation strategies:**
- Critical Care Societies Collaborative suggests that both organizational and individual (ICU professionals) role is important, and that clinicians should have "individual

accountability for maintaining their own emotional and physical health and for building resiliency". It includes several personal skills like identification of symptoms, developing healthy strategies of self-care, avoiding unhealthy behaviours, etc.

- Pilot studies of resilience training in ICU physicians and nurses have generated positive signal, and psychiatrist can make useful contribution to offer such training locally.

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Management of Medical Emergencies associated with psychotropic medications

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Abstract

As with other medications, psychotropics are associated with adverse effects as well. Some of the adverse effects may be serious and may lead the patient to seek care in the emergency services. The present guidelines cover many of the medical emergencies associated with psychotropic medications. Patients with these presentations may be encountered in emergency setting, other medical surgical wards, and in various psychiatric setting. The present guidelines provide an overview of approach to these medications related adverse effects which necessitate emergency management. Such individual emergencies are also discussed in terms of the causative psychotropic agents, the manifestations, and the management. These guidelines are not a substitute to the clinical knowledge and every patient presenting with these features will require individualized assessment and management. Yet, these guidelines are likely to benefit practising psychiatrists who encounter these emergencies in the clinical setting.

Introduction

Psychotropic medications are known to be associated with certain side effects that can present as medical emergencies. These include neuroleptic malignant syndrome, serotonin syndrome, anticholinergic syndrome, dystonia, akathisia, etc. For these conditions the etiological relationship of the side effect and the medical emergency is well established. Additionally, the use of psychotropic medications is also associated with other side effects, which may mimic a physical illness (Table-1). It is important to understand that for these side effects, at present, the data is available only in the form of association studies. Patients with these presentations may be encountered in emergency setting, other medical surgical wards, and in various psychiatric setting. All these presentations require immediate attention. These side effects are mostly considered as rare side effects, but when these occur and go unnoticed, then these could be fatal. The recognition of these side effects is usually not straight forward,

as the association of these side effects with psychotropic medications require ruling out of other possible causes and often the final conclusion is made after the acute crisis is resolved. The most common presentation of these side effects is altered sensorium, but depending on the side effect, the presentation can vary from difficulty in vision, to persistent erection, or non-specific symptoms like fever, fatigue, shortness of breath, palpitation, constipation, etc. Although most of these side effects are discussed in isolation in the literature, it is important to note that, many patients present with more than one of these rare side effects to the medical emergency. Hence, it is important to carry out a thorough evaluation to rule out all possible side effects and effectively manage the same. In most situations, detection of these side effects requires a high degree of clinical suspicion, taking a proper history, carrying a detailed physical examination and ordering routine and certain specific investigations. An important issue encountered in such situations is to continue/discontinue the psychotropics, and to determine which psychotropics should be used to address the primary illness, should they be required the in future.

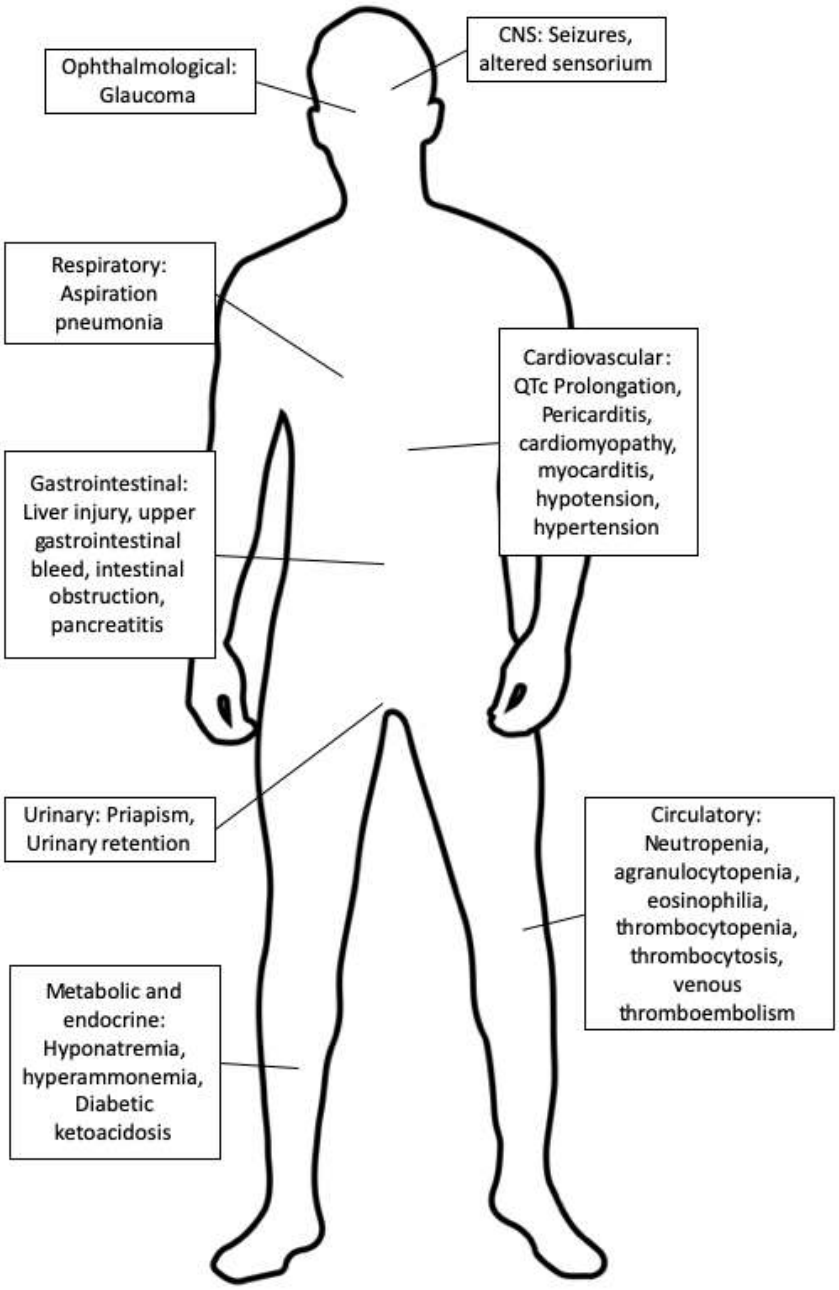
The present guidelines provide an overview for evaluation of patients presenting with medical emergencies associated with psychotropic medications. Figure 1 presents the typical organ systems affected by psychotropic medications which lead to emergency treatment seeking. These guidelines are not a substitute to the clinical knowledge and every patient presenting with these features will require individualized assessment and management. Certain other medical emergencies where the association with psychotropic medications is much better established (like acute dystonias, neuroleptic malignant syndrome, serotonin syndrome etc.) are discussed separately in another set of guidelines.

Table-1: Medical Emergencies associated with use of Psychotropic Medications

Medical Emergencies	**Commonly implicated medications**
Neurological	
1. Seizures	Antipsychotics, Antidepressants
Haematological	
2. Blood dyscrasias: agranulocytosis, thrombocytopenia, anaemia	Antipsychotics, Antidepressants, Mood stabilisers, Benzodiazepines
3. Thromboembolism	Antipsychotics, Antidepressants
Metabolic and Endocrine Related	
4. Hyponatremia	Antidepressants, Antipsychotics, Carbamazepine/ oxcarbamazepine, Valproate, lamotrigine, Benzodiazepines
5. Hyperammonemia	Valproate, Olanzapine
6. Diabetes Ketoacidosis	Antipsychotics
Pulmonary	

7. Aspiration pneumonia	Antipsychotics
Cardiac	
8. QTc prolongation and other cardiac conduction abnormalities	Antipsychotics, Antidepressants, lithium
9. Hypotension	Antipsychotics, Antidepressants
10. Hypertension	Antipsychotics, Antidepressants
11. Myocarditis	Antipsychotics
12. Cardiomyopathy	Antipsychotics
13. Pericarditis	Antipsychotics
Gastrointestinal and Hepatic	
14. Pancreatitis	Antipsychotics
15. Acute Liver Failure	Antipsychotics, Antidepressants, Mood stabilizers, Benzodiazepines
16. Gastrointestinal Bleeding	Antidepressants
17. Intestinal obstruction	Antipsychotics, Antidepressants
Genitourinary	
18. Priapism	Antipsychotics, antidepressants, Buspirone, methylphenidate, atomoxetine
19. Urinary retention	Antidepressants, Antipsychotics
Ophthalmological	
20. Glaucoma	Antidepressants, Antipsychotics
Dermatological	
21. Steven Johnson Syndrome, Toxic Epidermal Necrolysis	Antidepressants, Antipsychotics, Carbamazepine, Lamotrigine

Figure 1: Typical organ systems affected due to psychotropics which lead to treatment seeking in the emergency



Initial Assessment for establishing the Association and General Measures for Management

As discussed earlier, the diagnosis of psychotropics associated medical emergencies (such as aspiration pneumonia, myocarditis, cardiomyopathy, pancreatitis, hepatic failure, etc) requires a high index of suspicion and awareness of the clinicians about the possibility.

Whenever a patient with psychiatric disorder presents with symptoms and signs akin to any medical illness, a possibility of contribution of the ongoing psychotropic must be kept in mind. The most important aspect of evaluation includes establishing the relationship of the side effect with the ongoing psychotropic medication. A good history taking is of paramount importance in this regard. During the history taking the clinician should not only focus on anamnestic recall of facts, but should also review all the available treatment charts (including the investigations and the ongoing medications) (Table-2). The approach to patients with suspected medical emergency due to psychotropics is presented in figure 2. While history taking due importance should be given to any recent change in medications, which could be either addition or removal of a medication. This is important from the drug interaction point of view, because, removal of an inhibitor can lead to increase in the serum levels of the ongoing psychotropic medication and resultant side effect. The definite association is usually established based on the temporal association, available evidence in the literature for such an association, response to withdrawal of medication, and effect of rechallenge (Table-2). Due importance should be given to the change in the doses of ongoing medications, as some of the side effects may be dose related.

Additionally, a thorough physical examination should be carried out because it can provide important information about other side effects of the medications or other possible etiological factors responsible for or contributing to the clinical picture (Table-3). For example, fever may provide hint for infections.

All possible differential diagnosis in the form of other possible medical diagnosis associated with similar presentations and other medical emergencies (like, neuroleptic malignant syndrome, serotonin syndrome, anticholinergic syndrome, etc) associated with use of psychotropic medications must be considered.

The third component of establishing the association is ordering or reviewing the investigations as these may provide information about the possible association of side effect/clinical presentation with the psychotropics or other possible explanations. In all patients basic investigations must be carried out and any further investigations should be guided by the differential diagnoses considered, and advised by other clinicians.

The general management measures should focus on safety of the patient. Till the other possible cause is not established, it is better to stop/substitute the suspected ongoing psychotropic medication and other medications which may be contributing to the side effect (Table-4). However, discontinuation/substitution of non-psychotropic medications should be done in liaison with the concerned specialists, without destabilizing the medical condition.

Maintenance of airways, breathing and circulation is of paramount importance and appropriate measures must be taken to address the same.

The subsequent sections deal with the specific medical emergencies, their assessment and management.

Table-2: History taking in a patient presenting with a suspected side effects associated with the psychotropic medications

History

- **Review the clinical features and try to look for features specific to various medical emergencies**
- **Review the current psychiatric history including suicidal behaviour**
- **Review the history of intake of psychotropics in terms of starting of various medications, recent change in doses**
- **Review the history of physical comorbidities which are considered to be risk factors for various psychotropic associated medical emergencies:** Diabetes mellitus, hypertension, hypothyroidism, Obstructive Pulmonary Disease (COPD), cardiac failure, head injury, stroke, cirrhosis of liver, malignancies
- **Review the available treatment records:** for past history of similar acute medical emergencies and their association with the psychotropics
- **Review for other factors which could be contributing to the medical emergency**
- **To improve the detection of side effects, the physician should look for the anamnestic key factors listed below**
  - Dates of occurrence of psychiatric symptoms/seizures suspected of being side effects
  - Dates of medication exposure, dechallenge, and rechallenge
  - Previous psychiatric history
  - Dates of worsening of existing comorbidities
  - Other side effects of the same medications
  - Plasma concentration measurements
  - Dose of medication at which the side effects appeared
  - Any recent change in dose just prior to onset of side effects
  - Past history of exposure to medication and side effects at that time
  - Addition of any other medication close to onset of side effects, which can also lead to similar side effects
  - Compliance with medication
  - Effect of non-adherence on side effect (improvement/worsening)
  - If polypharmacy is given, dates of introduction or discontinuation of other drugs
- **Evaluate Concomitant medications & Drug interactions**
  - Could the side effect be an outcome of drug interactions or concomitant use of other medications

Comorbidity may also contribute to similar manifestations

- Physical illnesses themselves can have recurrence or a patient can have new onset physical illness

Could the manifestation be secondary to another side effect

- For example, hyponatremia leading to seizures

Good History Taking & Review of Treatment Charts:

- Emergence of any new metabolic abnormality which can explain the side effect(s)
- Worsening of primary illness, which can explain the emergence of side effect(s)

- Identify the probable factors which if not causative, may be contributory (concomitant medications, hospitalization, intensive care unit (ICU) stay, distress due to prolonged hospital stay, lack of sleep etc)

Factors determining causal relationships between medications and the possible side-effects

- Temporal relationship between the drug exposure and the side-effect
- Definitive pharmacological or phenomenological evidence of specific side-effects
- Presence or absence of alternative explanations for symptoms (e.g. disease, other drugs)
- Response to withdrawal of drug
- Effect of rechallenge with the same drug
- The diagnosis of a side effect being related to a medication should always be provisional- diagnosis is always confirmed after the resolution of the syndrome
- The most useful complementary examination for side effects investigation is generally the monitoring of plasma concentrations of suspected medications
- Use Naranjo's scale/WHO UMC scales to grade the association

Table-3: Physical examination and Basic investigations

Physical examination

- **Vitals:** heart rate, blood pressure, respiratory rate, temperature
- **Examination:** Chest examination, examination of cardiovascular system, examination of abdomen, and neurological examination to look for specific signs associated with the medical emergency

Mental Status Examination

- Assess for current severity of the psychiatric symptoms, association of symptoms (increase or decrease) with starting or change in the doses of medications, evaluate for delirium

Investigations (guided by the clinical presentation)

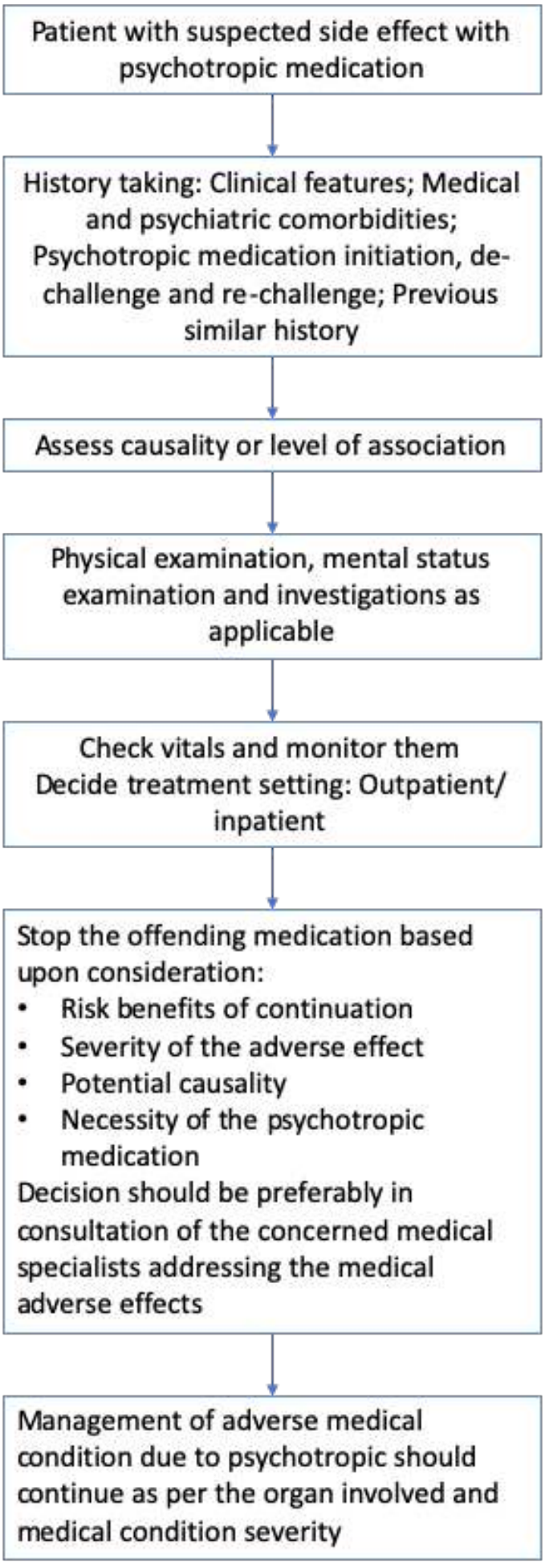
- Haemogram, Absolute Neutrophil Count
- Renal function test
- Liver function test
  - May provide information about the reduced clearance
  - May also be important while considering selection of psychotropics and other medications
- Blood glucose levels, lipid profile
- Serum electrolytes
  - Indicator of metabolic disturbance, can influence selection of antidepressants/antipsychotics/antiepileptics
- Neuroimaging
- Chest X-ray
- Electrocardiogram
  - May be important for selecting the psychotropic medications (QTc), if these are to be used in patients receiving other medications

Table-4: General Measures

General Measures

- Decide about the treatment setting: outpatient, inpatient (psychiatry/Medical-surgical ward), intensive care unit
- Review the whole prescription
- Stop the psychotropic considered to be associated with development of the particular medical emergency
- Look for all other possible modifiable contributing factors and decide about discontinuation/substitution in liaison with the concerned specialists, without destabilizing the medical condition
- Manage the Airways, breathing, and circulation
- Monitor vitals
- Stop all the unnecessary medications
- Stop the suspected psychotropic(s)

Figure 2: Flowchart for general assessment and management of psychotropic medication induced side effects


Patient with suspected side effect with psychotropic medication
History taking: Clinical features; Medical and psychiatric comorbidities; Psychotropic medication initiation, de-challenge and re-challenge; Previous similar history
Assess causality or level of association
Physical examination, mental status examination and investigations as applicable
Check vitals and monitor them
Decide treatment setting: Outpatient/ inpatient
Stop the offending medication based upon consideration:
• Risk benefits of continuation
• Severity of the adverse effect
• Potential causality
• Necessity of the psychotropic medication
Decision should be preferably in consultation of the concerned medical specialists addressing the medical adverse effects
Management of adverse medical condition due to psychotropic should continue as per the organ involved and medical condition severity

Seizures

Seizure is a medical emergency which is associated with use of various psychotropics in the therapeutic doses, or in toxic doses. Seizures can also occur as part of withdrawal syndrome associated with benzodiazepine or rapid tapering of benzodiazepine or antiepileptic agents. Seizures in patients on psychotropic could also be a secondary manifestation of other side effects of psychotropics (e.g., seizure secondary to hyponatremia). In this section we would limit ourselves to the discussion of seizures associated with use of psychotropics in therapeutic doses. Antidepressants associated with high risk of development of seizures include amoxapine, bupropion, clomipramine, maprotiline and mianserin. Among the antipsychotics, the highest risk of seizure is reported with clozapine and chlorpromazine (Table-5). In general, the risk of seizure is higher for Second Generation Antipsychotics (SGAs) compared to First Generation Antipsychotics (FGAs). Among the SGAs, higher risk is associated with clozapine, olanzapine and quetiapine.[1] Various risk factors have been reported to predispose to development of seizures. Among the various risk factors (Table-6), use of higher dose of psychotropics is reported to be one of the most important risk factor.

Table-5: Psychotropics and seizures[2,3]

High Risk	Intermediate Risk	Low Risk
Antidepressants Amoxapine Bupropion Clomipramine Maprotiline Mianserin Imipramine in higher doses	Amitriptyline Imipramine	SSRIs Trazadone Venlafaxine MAOI Mirtazapine
Antipsychotics Chlorpromazine (dose related) Clozapine (titration & dose related)	Haloperidol	Fluphenazine Trifluoperazine Risperidone Olanzapine Quetiapine

Table-6: Risk factors for seizures[3,4]

Patient related predisposing factors associated with psychotropic associated seizures
• History of epilepsy (including febrile convulsions) in the patient and/or their family • Presence of neurological abnormalities (brain injury, interrupted blood brain barrier), cerebral atherosclerosis • Pre-existing EEG alterations • Presence of general physical illnesses (e.g. malignant hypertension leading to hypertensive encephalopathy)

- HIV/AIDS
- CNS infection
- Pre-existing EEG alterations
- Elderly age group
- Reduced drug clearance
- Impaired renal or hepatic functioning
- Substance abuse
- Alcohol abuse

Drug related predisposing factors associated with psychotropic associated seizures

- Polypharmacy
- Higher doses
- Rapid titration
- Abrupt withdrawal
- Abrupt dose changes
- Prolonged treatment
- High serum levels

In terms of clinical manifestations, psychotropic associated seizures may present as myoclonus, focal seizures or generalized seizures. Accordingly, the patients may present to emergency with generalized tonic clonic seizures, or report of jerks. While taking history, besides the general issues as discussed earlier (Table-2) the clinician should focus on frequency, typology and past history of seizures. Additionally, while taking history, importance must be given to the doses of psychotropics used, any recent change in the doses, any addition or removal of any medication from the prescription and other aspects as listed in table-2 and table-7.

In terms of differential diagnosis, other medical and neurological disorders should be considered and history taking and physical examination should focus on ruling out the same (Table-7). Some of the common differential diagnosis can include meningitis, encephalitis due to any cause, other central nervous system infections, metabolic disturbances leading to seizures, stroke, and any kind of brain tumors. It is always advisable to rule out these possibilities and to consider neuroimaging in patients presenting with seizure. Other investigations like cerebrospinal fluid analysis, autoimmune panel, etc should be done in liaison with other specialists (Table-8).

In terms of management, besides the general measures (Table-4), the first step involves stopping/reducing the offending agent. If a patient presents with status epilepticus than the first aim should be control the seizures and in such a situation loading doses of antiepileptics (phenytoin or levetiracetam) should be considered. In patients presenting with isolated seizures, if this is not possible then reduction in the dose of the offending agent should be

considered, without compromising the efficacy. If there is no alternative to the offending agent, then addition of antiepileptic medication should be considered (Table-9). While choosing antiepileptic agents, issues of drug interactions and synergistic side effects, and effect of the antiepileptic on the psychiatric disorder must be kept in mind.

Table-7: Specific issues in history taking and physical examination while evaluating the association of side effects with psychotropics

Side effects	History and clinical presentation	Physical Examination
Seizures	• Seizures: frequency, typology, past history • Medication adherence • All medications taken: prescription and over the counter • Use of substances, including recent abstinence or intoxication • Can the seizure be attributed to the withdrawal or intoxication of the ongoing medication • Any recent suicidal behaviour • Evaluate the relationship of seizure with change in the – Complications arising due to the illness per se – Changes in the metabolic profile • Intake of other medications with higher risk of seizures	• Evaluate for neurological deficits • Evaluate for signs of meningitis • Look for other features of drug toxicity, neuroleptic malignant syndrome, anticholinergic syndrome
Glaucoma	• Severe headache • Nausea • Vomiting • Pain the eyes • Blurring of vision • Redness in eyes • Halos around the lights.	• Size of the pupil (mid-size) • Slit lamp examination • Check the intraocular pressure (IOP) • Gonioscopy
Neutropenia	• Fever, chills, or sweating • Features of infection: sore throat, cough or shortness of breath, burning micturation, loose motion	• Evaluate for fever • Look for signs and symptoms of infection • Look for other conditions which can cause neutropenia
Agranulocytopenia	• Fever, chills, or sweating • Fatigue • Bleeding gums • Features of infection: sore throat, cough or shortness of breath, burning micturation, loose motion	• Evaluate for fever • Look for signs and symptoms of infection • Look for other conditions which can cause agranulocytopenia

Eosinophilia	• Rash • Itching • Diarrhoea • Respiratory symptoms • Pain abdomen • Skin lesion (drug reaction with eosinophilia and systemic symptoms [DRESS])	• Evaluate for respiratory symptoms, features of pancreatitis, myocarditis, colitis, hepatitis • Evaluate for features of DRESS syndrome • Look for other conditions which can cause eosinophilia
Thrombocytopenia	• Bleeding gum • Petechiae • Purpura • Blood in urine/stool	• Look for all signs and symptoms of bleeding • Look for other conditions which can cause Thrombocytopenia
Thrombocytosis	• Headache • Dizziness • Chest pain • Fatigue and/or weakness • Numbness or tingling of the hands and feet	• Look for other conditions which can cause Thrombocytosis
Venous thromboembolism	• Leg pain or tenderness in the thigh region • Leg swelling, or reddish discoloration of the skin, and raised temperature in the local area • Pulmonary thromboembolism may manifest with shortness of breath, tachypnea, tachycardia and chest pain.	• Look for leg swelling, skin temperature, tenderness • Respiratory symptoms
Hyponatremia	• Headache • Confusion • Muscle cramps • Lethargy • Severe agitation • Seizures • Delirium • Stupor • Chenyne stokes breathing • Coma	• Evaluate the sensorium • Look for features of delirium • Deep tendon reflexed: diminished • Evidence of ataxia • Hydration status • Evidence for seizure
Hyperammonemia [5,6]	• **Nonspecific symptoms:** acute onset lethargy, headache, dizziness, tiredness • **Gastrointestinal symptoms:** nausea, vomiting, constipation, loss of appetite • **Neurological symptoms:** tremor, myoclonus, extrapyramidal symptoms, parkinsonism, ataxia, adiadochokinesia along with	• Detailed neurological examination • Assess the level of sensorium

	asterixis, slurred/illogical/bizarre speech, blurred vision, focal neurological deficits, seizures • **Behavioural symptoms**: feeling slowed, sleep related issues (drowsiness, sedation, hypersomnia), altered mental state examination findings (such as decreased alertness, confusion, unconsciousness, obtundation, disorientation, forgetfulness, catatonia, irritability, psychomotor agitation) • **C**oma	
Diabetic Ketoacidosis	• History of recent weight changes (gain/loss), polyuria, polydipsia, polyphagia • Weakness • Fruity breath • Nausea • Vomiting with coffee-ground content • Dehydration • Altered sensorium	• Fruity breath • Assess the level of sensorium • Hydration status
Aspiration pneumonia	• Cough with or without expectoration • Difficulty in breathing • Fever • Fatigue • Nausea • Vomiting • Diarrhoea • Respiratory failure	• Fever or hypothermia • Tachycardia • Tachypnea • Dullness to chest percussion in the areas of consolidation • Pleural rub • Hypotension • Altered sensorium or delirium • Bad breath
QTc Prolongation	• Light headedness • Palpitation • Syncope	• Monitor the vitals • Manage the airways • Features of dehydration
Hypotension	• Dizziness • Light-headedness • Headache • Visual disturbance • Generalized weakness	• Assess vitals • Manage the airways • Features of dehydration • Assess for postural fall
Hypertension	• Headaches especially in the early morning • Epistaxis • Visual disturbances • Buzzing sound in the ears • Nausea	• Assess vitals • Assess blood pressure

	• Vomiting • Anxiety • Chest pain • Fatigue • Confusion	
Myocarditis	• Fever • Flu like symptoms • Nausea • Dizziness • Tachycardia • Tachypnea • Chest discomfort • Hypotension	• Assess vitals • Manage the airways • Assess blood pressure • Detailed cardiovascular and respiratory evaluation
Cardiomyopathy	• Increasing breathlessness (most common symptom) • Orthopnoea • Paroxysmal nocturnal dyspnoea • Tachycardia • Palpitations • Chest pain • Fatigue	• Assess vitals • Manage the airways • Assess blood pressure • Detailed cardiovascular and respiratory evaluation • Look for peripheral oedema • Evidence of raised jugular venous pressure
Pericarditis	• Flu-like symptoms • Fever • Tachycardia • Diarrhea • Gastrointestinal symptoms • Chest pain • Shortness of breath • Dyspnea	• Assess vitals • Manage the airways • Assess blood pressure • Detailed cardiovascular and respiratory evaluation
Drug Induced Liver Injury	• History: Concomitant medication intake • Exposure to toxins • Use of alcohol • Fatigue • Malaise • Loss of appetite • Epigastric discomfort • Pain in the right hypochondria • Jaundice • Itching • Arthralgia • Abdominal swelling • Nausea • Vomiting • Altered sensorium	• Features of jaundice • Sweet or musty breath odour • Other features of liver failure: ascites • Altered sensorium or delirium

Upper Gastrointestinal Bleeding[7,8]	• Concomitant medication intake: aspirin, clopidogrel, warfarin • Past history of upper gastrointestinal bleed. • Bleeding for any other site • History of smoking, alcohol intake • Pain in the abdomen • Hematemesis	• Features of anaemia • Look for bruises • Any other signs of bleeding
Intestinal Obstruction-Paralytic Ileus	• Review history of use of other medications which can cause constipation • Last passage of stool • Passage of flatus • Constipation • Pain abdomen • Vomiting	• Abdominal examination: abdominal distension, tenderness, reduced or absent bowel sounds • Vitals: Hypotension, tachypnoea, tachycardia, fever • Features of septic shock
Pancreatitis [9]	• Pain abdomen (epigastric pain, radiating to back) • Fever, tachycardia • Concomitant use of medications: statins, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitor enzyme, retroviral therapy, etc. • Substance abuse: alcohol, cannabis, cocaine, opioids • Rule out other causes like gall stones, hypertriglyceridemia, hypocalcemia, trauma, recent Endoscopic retrograde cholangiopancreato-graphy (ERCP) intervention, autoimmune causes	• Abdominal examination-tenderness, muscle guarding, • Evidence of jaundice • Respiratory distress • Altered sensorium
Priapism[10,11]	• Duration of erection • Level of pain • History of priapism, prolonged painful erections in the past • Ongoing medications • Use of erectorgenic medications in the recent past • Drug abuse- especially opioids • History of sickle cell anaemia or other hemoglobinopathies • History of hypercoagulable states • Trauma to the local area	• Proper examination of genitalia, perineum, and abdomen • Examine the penis (in ischemic priapism, the glans will be soft, but the corpora is fully rigid and tender) • Look for any signs of trauma, malignancy
Urinary retention [12]	• Duration of urinary retention	• General signs of

	• Past history of urinary retention • Signs and symptoms of different urinary tract infections	infection: inspection, palpation, • Local examination: examination of genitilia, per-rectal examination, tenderness • Percussion over the bladder • Neurological examination

Table-8: Investigations specific for the suspected medication associated emergency

Medical Condition	Specific Investigations
Seizures	• Electroencephalogram (EEG) • Neuroimaging • Cerebrospinal fluid analysis: in cases where meningitis, and encephalitis are differential diagnosis • Serum levels of drugs if required
Glaucoma	• Slit lamp examination • Tonometry: to check the intraocular pressure (IOP) • Gonioscopy • Ophthalmoscopy • Visual fields • Ultrasound biomicroscopy
Neutropenia	• Haemogram • Complete blood count • Blood film • Bone marrow biopsy • Other investigations guided by differential diagnosis and clinical manifestations (i.e., site of infection)
Agranulocytosis	• Haemogram • Complete blood count • Blood film • Bone marrow biopsy • Other investigations guided by differential diagnosis and clinical manifestations (i.e., site of infection)
Eosinophilia	• Haemogram • Complete blood count • Blood film • Bone marrow biopsy • Other investigations guided by differential diagnosis and clinical manifestations (i.e., site of infection) • Look for possible underlying conditions associated with use of medications presenting with eosinophilia: pancreatitis, myocarditis, colitis, pleural effusion, hepatic failure

Thrombocytopenia	• Haemogram • Complete blood count • Ultrasound abdomen to look for size of spleen • Blood film • Bone marrow biopsy • Other investigations guided by differential diagnosis and clinical manifestations (i.e., site of infection, dengue fever)
Thrombocytosis	• Haemogram • Complete blood count • Blood film • Bone marrow biopsy • Other investigations guided by differential diagnosis and clinical manifestations (i.e., site of infection)
Venous thromboembolism	• Compression ultrasound/ duplex ultrasonography • Magnetic resonance Imaging • Plethysmography • Venography • International Normalised Ratio (INR) • Compression stocking • If pulmonary embolism is suspected: computed tomographic pulmonary angiography, ventilation-perfusion (V/Q) scan, pulmonary angiography, magnetic resonance imaging
Hyponatremia	• Serum sodium levels • Other serum electrolytes • Urinary sodium (> 30mEq/L indicates SIADH) • Urinary osmolality (>100mEq/L indicates SIADH) • Electrocardiogram • Blood glucose levels, lipid profile, serum protein levels • Renal Function tests, liver function test • Investigations to rule out other differential diagnosis • Neuroimaging: if central pontine myelinolysis is suspected
Hyperammonemic encephalopathy [5]	• Serum Ammonia levels • EEG, MRI, CT • Serum glutamate levels • Serum carnitine levels • Investigations for evaluating the defect in urea cycle: ornithine transcarbamylase (OTC) deficiency
Diabetic Ketoacidosis [13]	• Hba1c • Urine ketones • Serum ketones • Effective serum osmolality (mOsm/kg) • Anion gap (mEq/L)
Aspiration Pneumonia	• X-ray chest

	• Arterial blood gas analysis • Sputum for culture • Blood culture • Haemogram including the TLC and differential count • Other investigations like HRCT, bronchoscopy, thoracocentesis: guided by differential diagnosis and severity
QTc prolongation	• Electrocardiogram (ECG) • Serum electrolytes (potassium, magnesium)
Hypotension	• Electrocardiogram (ECG) • Serum electrolytes (potassium, magnesium)
Hypertension	• Electrocardiogram (ECG) • Serum electrolytes (potassium, magnesium) • Evaluate for other causes of hypertension • Evaluate for complications of hypertension
Myocarditis [14]	• Haemogram (may show evidence of eosinophilia), • C-reactive protein (CRP) • Troponin T and I • Creatine kinase-MB (CK-MB) • B-type natriuretic peptide (BNP) • N-terminal fragment of pro-BNP (NT-pro-BNP) • Interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) levels • ECG • Transthoracic echocardiography (TTE) • Cardiac magnetic resonance imaging (CMRI)
Cardiomyopathy	• Transthoracic Echocardiography: dilated and thin-walled LV with systolic impairment • ECG changes • B-type natriuretic peptide (BNP) • N-terminal fragment of pro-BNP (NT-pro-BNP) • Cardiac MRI
Pericarditis	• ECG • Creatine phosphokinase-MB levels • CRP levels • Troponin levels • Echocardiography
Drug induced liver injury	• Liver function test • Haemogram, absolute eosinophil count • Ultrasound abdomen • Other investigations based on differential diagnosis and complications: viral markers, CT/MRI of the abdomen, Liver biopsy
Upper Gastrointestinal Bleeding	• Blood grouping • Upper gastrointestinal endoscopy • Bleeding and clotting time
Intestinal obstruction-Paralytic	• X-ray Abdomen and Pelvis

ileus	• Ultrasound abdomen
Pancreatitis	• Ultrasound abdomen • Imaging: computerised tomography of abdomen • Magnetic resonance cholangio-pancreatography • Serum amylase, lipase, alkaline phosphatase • Lipid profile • Serum calcium • Immunoglobulin levels (Ig) IgG4 levels
Priapism	• Coagulation profile • Corporal blood gas analysis (will aid in distinguishing arterial and ischemic priapism)
Urinary retention	• Renal function test, serum electrolytes, serum glucose levels • Urine-routine and microscopy • Ultrasound: abdomen and pelvis • MRI brain and MRI spine (if neurological causes are considered) • Cystoscopy, cysto-urethroscopy • Urodynamic studies

HRCT High Resolution Computed Tomography, SIADH Syndrome of inappropriate antidiuretic hormone secretion

Table-9: Specific interventions for the suspected medication associated emergency

Medical Condition	Specific interventions	Prevention of the side effects
Psychotropic related seizures	• Step-1: Stopping the offending agent should be considered as the first option, if feasible • Step-2: If not feasible, reduction in dose, without compromising the efficacy should be considered • Step-3: If there is no alternative to the offending agent, then addition of antiepileptic medication should be considered	• Use of medications with lower risk of seizures • Use of agents which have least impact on seizure threshold
Glaucoma	• Stop the offending agent • Medical therapy for acute glaucoma: topical β-blocker, α_2-agonist, prostaglandin analogues • Surgical intervention: laser peripheral iridotomy, determined by the severity of symptoms	• Avoid use of medications with high anticholinergic and adrenergic agents in vulnerable groups • Regular ophthalmological review
Neutropenia	• Stop the offending agent • Monitor the neutrophil count • Absolute neutrophil count • Continuation/discontinuation decided based on severity of neutropenia • Colony stimulating factor in patients	• Regular monitoring of haemogram • Making patient aware about the clinical features

	with severe neutropenia • Manage the secondary infection	
Agranulocytosis	• Stop the offending agent • Monitor the platelet count • Continuation/discontinuation decided based on severity of agranulocytosis • Colony stimulating factor in patients with severe neutropenia • Manage the secondary infection	• Making patient aware about the clinical features • Making patient aware about the clinical features
Eosinophilia	• Stop the offending agent • Monitor the eosinophil count • Continuation/discontinuation decided based on severity of eosinophilia • Manage the secondary infection • Other measures depends on systemic involvement	• Making patient aware about the clinical features
Thrombocytopenia	• Stop the offending agent • Monitor the platelet count • Continuation/discontinuation decided based on severity of thrombocytopenia	• Making patient aware about the clinical features
Thrombocytosis	• Stop the offending agent • Monitor the platelet count • Continuation/discontinuation decided based on severity of thrombocytosis	• Making patient aware about the clinical features
Venous Thromboembolism	• Stop the offending agent • Serial compression ultrasound • Unfractionated IV heparin	• Monitor the International Normalised Ratio (INR)
Hyponatremia [15]	• Stop the offending agent(s) • Monitor serum sodium levels daily till serum sodium levels normalize • Mild hyponatremia: discontinuation of the drug and if this does not lead to an increment in the serum sodium level, water restriction (0.5 to 1 L/day) should be considered • Moderate to severe: discontinuation of the offending agent, water restriction (0.5 to 1 L/day), if neurological signs and symptoms are present then correction with hypertonic saline is indicated • 3% hypertonic saline administered at the rate of 1 mL/kg/h until clinical improvement and serum sodium increases by 4 to 6 mEq/L (The rate of correction of hyponatremia should not exceed a maximum of 10 to 12	• Making patient aware about the side effect and the clinical features • Use agents which have lower potential to cause hyponatremia to manage the primary psychiatric condition • Monitor serum sodium levels in high risk groups, during the initial phase of treatment, especially when the doses are being increased

	mEq/L in 24 hours in patients with severe hyponatremia • A bolus dose of hypertonic saline (100 mL of 3% saline) to be considered in patients with seizure or in coma • Avoid rapid correction of serum sodium as this can lead to central pontine myelinolysis	
Hyperammonemic encephalopathy [5]	• Stop the implicated agent • Improve hydration • Protein restriction • Monitor serum glucose levels and take appropriate measures • Lactulose/rifaximin/neomycin • L-carnitine • Severe encephalopathy: furosemide, acetaglutamide, mannitol to reduce cerebral edema • N-carbamylglutamate (NCG) if the patient has N-acetylglutamate (NAG) synthetase deficiency • Dialysis if the serum ammonia level is between 300-500 μmol/L	• Low protein diet in patients with liver disease • Avoiding use of alcohol
Diabetic Ketoacidosis	• Maintain hydration • Maintain serum electrolyte levels • Insulin • Monitor serum glucose levels	• Using agents with lower potential to cause raised blood glucose levels • Monitoring of serum glucose levels at regular intervals in patients on antipsychotics and other agents associated with weight gain
Drug induced liver injury	• Remove the offending agent(s) • Use of liver protective agents	• Check for all the medications which the patient is taking • Avoid alcohol
Aspiration pneumonia	• Remove the offending agent(s) • Oxygen support as per the requirement • Pulse oximetry • Monitor the cardiac parameters • IV assess and fluids as per the requirement • Antibiotics • Maintain hydration • Management of complications	• Avoid polypharmacy • Encourage the patient to abstain from smoking and alcohol • If a patient has respiratory disease, than manage the same appropriately • Address the neurological comorbidities • Avoid malnutrition • Use the minimum effective doses of

		medications • Avoid inappropriate and prolonged use of gastric acid secretion suppressors
QTc prolongation	• Removing/reducing the offending agent • Use of IV magnesium/potassium • Anti-arrhythmic agents • Cardioversion	• Baseline ECG and monitoring the ECG and potassium • Slow escalation of the doses, especially of medications which have higher risk • Patient need to be psychoeducated to report immediately, if they have new symptoms in the form of palpitation, lightheadedness, syncope, etc. • Avoid medications which have high risk of QTc prolongation
Hypotension	• If the symptoms are mild, reduce the dose of the offending agent • If the symptoms are severe and life-threatening stop the offending agent • Abdominal binders • Compression leg stocking • Increase fluid intake	• Avoid sudden change in the posture • Avoid physical activity, intake of alcohol, carbohydrate rich food, and exposure to heat • Use abdominal binders • Compression stocking • Adequate fluid intake
Hypertension	• Stop the offending agent	• Low salt diet • Healthy diet • Regular physical exercises • Avoid smoking and alcohol • Adequate sleep
Myocarditis	• Stop the offending agent • Stabilize the cardiac status • Corticosteroids • Diuretics, beta-adrenergic blockers • Angiotensin-converting enzyme (ACE) inhibitors • Angiotensin II receptor blockers (ARBs)	• Baseline investigation and assessments: Troponin (T or I), CRP levels, ECG, echocardiography, heart rate, temperature, blood pressure • Monitor daily: Fever, chest pain, dyspnoea, myalgia, headache, cough, diarrhoea, vomiting, etc • Monitor every 2 days:

		Pulse, blood pressure, respiratory rate, temperature • Every 7 days: Troponin (T or I), CRP levels
Cardiomyopathy	• Stop the offending agent • Stabilize the cardiac status • Corticosteroids • Diuretics, beta-adrenergic blockers • Angiotensin-converting enzyme (ACE) inhibitors	• Monitor the cardiac status
Pericarditis	• Stop the offending agent • Stabilize the cardiac status	• Monitor the cardiac status
Upper Gastrointestinal Bleeding (Andrade & Sharma, 2016; Stanley &Laine, 2019; Bixby et al, 2019)	• Remove the offending agent(s) • Review the concomitant medications and discontinue/substitute the medication in liaison with the specialist • Endoscopy	• Concomitant use of proton pump blocker • Making the patient aware about the side effect • Weigh the risk and benefits of using antidepressants in high risk groups • Avoid unnecessary use of NSAIDs
Intestinal Obstruction-Paralytic Ileus	• Stop the offending agent • Supportive management • In case of perforation: surgical intervention may be required	• Encourage patients to monitor the bowel habits • Encourage patients to consume high fibre diet, take adequate fluids and exercise regularly
Pancreatitis	• Remove the offending agent(s) • Achieve haemodynamic stability • Antibiotics	• Avoid using the same agent or agents reported to be associated with pancreatitis
Priapism (Hwang & Shah, 2020; Salonia et al, 2014)	• Remove the offending agent(s) • Step-1: Penile aspiration to decompress the corpora cavernosa; continue aspiration till fresh red blood is aspirated • Step-2: If the symptoms persist than give phenylephrine by diluting it normal saline (100-500 µg/mL concentration) and administered in the dose of 1 ml every 3-5 minutes in the corpus cavernosa with a maximum dose of 1 mg over 1 hour, with close monitoring of vitals • Step-3: Surgical intervention (penile shunt surgery)	• Decrease the dose or change the offending agent • Change to an agent with low alpha-adrenergic antagonist activity
Urinary Retention	• Stop/reduce the dose of the offending	• Have an understanding

	agents • Immediate catheterization to relieve the retention	about the receptor profile of various medication which the patient may be receiving and avoid drugs with high anticholinergic properties and adrenoreceptor agonists needs to be avoided in vulnerable patients • Avoid polypharmacy with agents with high anticholinergic properties and adrenoreceptor agonists

Glaucoma

Acute angle closure glaucoma can be an ophthalmological emergency associated with use of some of the psychotropic medications. If not identified in time, the sustained raised intraocular pressure can lead to irreversible axonal damage within the retinal nerve fibre layer and the optic nerve, resulting in irreversible blindness.[16] The blockage of pupil by the psychotropics is usually mediated by adrenergic or anticholinergic properties, or by idiosyncratic non-pupillary blockage. The medications commonly implicated for the acute angle closure glaucoma include the TCAs (associated with anticholinergic side effects), MAOIs, phenothiazine and other antipsychotics (associated with high anticholinergic side effects), benzodiazepines, topiramate, SSRIs (paroxetine, citalopram, escitalopram, fluoxetine, fluvoxamine) and Selective Norepinephrine Reuptake Inhibitors (SNRIs).

While starting various psychotropics the clinicians should be aware of the risk factors for angle closure glaucoma (Table-10) and preferably medications with lower risk of angle closure glaucoma should be chosen.

Acute angle closure glaucoma can present with sudden loss of vision, pain in the eye, redness of eyes, headache, blurring of vision, low vision, tunnel vision, seeing halos around the lights and red eyes. Additionally, the patients can also have systemic symptoms like nausea and vomiting.[16]

The initial assessment should include review of the symptoms. Investigations should focus on assessment of intraocular pressure. Other investigations are determined by severity of the symptoms (Table-8). Management involves reduction in the doses or removal of the offending agent (Table-9).

Table-10: Risk factors for acute angle-closure glaucoma[16–18]

- Race (Inuit, Asian and Hispanic are at highest risk)
- Narrow angle (of anterior chamber)
- Shallow anterior chamber depth
- Hyperopia
- Thin central part of cornea
- Small eye (nanophthalmos)
- Previous angle closure in fellow eye
- Family history of angle closure glaucoma
- Age >60 years
- Female sex
- Use of any substance that causes papillary dilatation/excitatory situations
- Medical comorbities: diabetes, heart disease, high blood pressure and sickle cell anaemia
- History of trauma to the eye

Psychotropics and blood dyscrasias

Various psychotropics have been shown to be associated with blood dyscrasias like agranulocytosis, neutropenia, thrombocytopenia, anaemia, eosinophilia, thrombocythemia, etc. Most of the data for this association is in the form of case reports/case series and retrospective studies. Among the various psychotropics, blood dyscrasias are more commonly reported with the use of clozapine. However, it is important to remember that these side effects are not limited to clozapine only, and others drugs (Table-11) can also cause blood dyscrasias. Different mechanisms have been reported to be responsible for these side effects.[19] The incidence of various haematological side effects with clozapine is reported to be: 0.38-22% for agranulocytosis, neutropenia 0.9-22%, eosinophilia 0.2 to 61.7%, thrombocytopenia 4.8-17.8%.[20] An important fact to note is that small sample size studies report higher incidence of blood dyscrasias with clozapine, and as the sample size increases the reported incidence reduces. A study from India reported the incidence of eosinophilia with clozapine to be 9.9%, thrombocytopenia to be 8.2%, neutropenia to be 0.6% and anaemia to be 2.2%. [20] The reported incidence rates for other psychotropics are relatively low.

In terms of clinical manifestations, many of these drug-induced blood dyscrasias may be asymptomatic and are detected only on investigation. However, when symptomatic, these may present with vague or non-specific clinical features (Table-11). An important fact to note is that clozapine associated eosinophilia may be associated with myocarditis, pancreatitis, colitis, toxic hepatitis and pleural effusion. Clozapine associated eosinophilia has also been reported to predict development of neutropenia.[21] Clozapine associated eosinophilia is also reported to be associated with pleural effusion, pancreatitis, myocarditis, colitis, hepatitis.[21]

In terms of differential diagnosis, all possible causes of these abnormalities should be

considered and ruled out on the basis of proper history, findings of physical examination and investigations.

There are no clear-cut guidelines for management of neutropenia associated with other psychotropics other than clozapine. However, when these abnormalities are detected, it is better to stop the suspected offending agent, till the definite cause is not established. For clozapine associated mild neutropenia (1000-1500/microL), stopping clozapine is not recommended. It is suggested that neutrophil count should be monitored thrice weekly till the absolute neutrophil count reaches more than 1500/microL. In case the patient presents with moderate neutropenia (500-1000/microL), then stopping of clozapine is recommended and daily monitoring of absolute neutrophil count is to be done till it reaches till>1000/microL, and then monitor thrice weekly till absolute neutrophil count >1500/microL and then weekly for 4 weeks. If the patient presents with severe neutropenia (<500/microL), then clozapine should be stopped, and granulocyte-colony stimulating factor (G-CSF) should be started in consultation with hematologist and re-exposure to clozapine should be avoided in persons presenting with severe neutropenia.[22]

Other measures involving management of haematological abnormalities should focus on management of infections if present, prevent bleeding and blood loss and any kind of thrombosis.

Table-11: Blood dyscrasias with various psychotropics[19,23–26]

Side effect	Implicated Medications	Common Clinical Presentations
Agranulocytosis	• Chlorpromazine, prochlorperazine, promazine, fluphenazine, haloperidol, thioridazine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone • Tricyclic antidepressants (amitriptyline/nortriptyline, imipramine, desipramine, clomipramine), tranylcypromine, mirtazapine • Carbamazepine • Chlordiazepoxide, diazepam	• Fever • Sudden onset malaise • Infection involving any part of the body
Neutropenia	• Chlorpromazine, prochlorperazine, promazine, fluphenazine, haloperidol, thioridazine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, lurasidone • Tricyclic antidepressants (amitriptyline/nortriptyline,	• Low grade fever • Sore throat • Infection involving any part of the body

	imipramine, desipramine, clomipramine, doxepine), tranylcypromine, citalopram, mirtazapine, nefazodone, venlafaxine, trazadone, venlafaxine • Valproate • Clonazepam, lorazepam	
Leucocytosis	• Haloperidol, fluphenazine, clozapine, risperidone, olanzapine • Citalopram, trazadone, venlafaxine • Carbamazepine, lithium	• Fever • Infection involving any part of the body
Leucopenia	• Carbamazepine, gabapentin	• Fever
Anaemia (aplastic, haemolytic)	• Chlorpromazine, risperidone, clozapine, lurasidone • Tranylcypromine, citalopram, sertraline, mirtazapine, nefazodone, trazadone, venlafaxine • Carbamazepine, lamotrigine, valproate • Chlordiazepoxide, clonazepam, diazepam	• Easy fatigability • Low energy levels • Shortness of breath • Dyspnoea on exertion • Tachycardia • Poor attention and concentration • Dizziness • Pale skin • Pallor
Eosinophilia	• Chlorpromazine, fluphenazine, clozapine • Tricyclic antidepressants (amitriptyline/nortriptyline, imipramine, desipramine) • Carbamazepine	• Fever • Skin rash
Thrombocytopenia	• Chlorpromazine, prochlorperazine, promazine, fluphenazine, thioridazine, haloperidol, trifluoperazine, methotrimeprazine, clozapine, olanzapine, quetiapine, risperidone, lurasidone • Tricyclic antidepressants (amitriptyline/nortriptyline, imipramine, desipramine, clomipramine), tranylcypromine, sertraline, mirtazapine • Carbamazepine, lamotrigine, valproate • Chlordiazepoxide, clonazepam, diazepam	• Fatigue • Heavy menstrual flows • Blood in urine or stools • Easy or excessive bruising (purpura) • Superficial skin bleeding (petechiae) • Prolonged bleeding from injury • Bleeding from different sources
Thrombocytosis	• Clozapine, lithium	• Headache • Dizziness • Weakness • Numbness or tingling of hands and feets
Lymphopenia	• Clozapine	• Infection involving any

		part of the body
Pancytopenia	• Fluphenazine • Clomipramine, mirtazapine • Lamotrigine • Diazepam	• Fever • Infection involving any part of the body
Pure Erythrocyte aplasia	• Carbamazepine, lamotrigine, valproate	• Influenced by the severity of anaemia
Impaired platelet Aggregation	• Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline • Chlordiazepoxide, diazepam	• Bleeding
Disseminated intravascular aggregation	• Fluoxetine	• Thromboembolism

Thromboembolism

Many psychotropics have also been shown to be associated with development of thromboembolism and this can manifest as venous thromboembolism or pulmonary thromboembolism. The available data suggest the association of thromboembolism with both first-generation antipsychotics and second generation antipsychotics (SGAs), with risk higher for the later group of antipsychotics. The antipsychotics that have been linked to thromboembolism include chlorpromazine, haloperidol, prochlorperazine, clozapine (possibly higher risk than other antipsychotics), olanzapine, and risperidone.[27,28] Although there is data in the form of case reports linking the association of antipsychotics like quetiapine, large scale data does not confirm the same.[27,28] Aripiprazole has been in general not reported to be associated with increased risk of thromboembolism.[27,28]

Similarly, use of antidepressants, i.e. tricyclic antidepressants, SSRIs and other antidepressants have also been shown to be associated with increased risk of development of venous thromboembolism.[29]

In this regard it is important to be aware of the risk factors commonly associated with development of venous thromboembolism and while prescribing antipsychotics, the clinicians should take these factors into consideration. These factors include immobilisation due to any cause, receiving hormonal therapy, obesity, higher age, presence of varicose veins or venous insufficiency, dehydration and thrombocytophilia.[27]

The venous thromboembolism may present with leg pain or tenderness in the thigh region, leg swelling, or reddish discoloration of the skin, and raised temperature in the local area. The pulmonary thromboembolism manifests in the form of shortness of breath, tachypnea, tachycardia and chest pain. In terms of management, the offending agent(s) should be stopped, and as with other drug induced conditions other possible causes must be ruled out.

Once diagnosed, thrombolysis with intravenous unfractionated heparin should be started with close monitoring of international normalized ratio (INR).

Hyponatremia

Hyponatremia is one of the common electrolyte imbalance reported to be associated with the use of psychotropics of various classes. Among the various psychotropics hyponatremia is often reported in patients on antidepressants (mainly SSRIs), followed by carbamazepine, and antipsychotics. Hyponatremia has been rarely also noted with the use of benzodiazepine/ anxiolytic. The incidence rates of hyponatremia with various psychotropics vary widely, mainly influenced by the sample size, and the cut-off value of sodium used to define hyponatremia. The incidence rates of hyponatremia with SSRIs vary from 0.06 to 40%,[30] with studies based on larger sample size reporting lower incidence rates. Studies which have compared various antidepressants suggest that the incidence rate of hyponatremia is lower with TCAs, when compared to SSRIs. In terms of antipsychotics, there is data in the form of case reports or small observational studies which have reported the association of hyponatremia with risperidone, quetiapine, olanzapine, aripiprazole, and clozapine. In terms of first-generation antipsychotics hyponatremia has been reported to be associated with the use of phenothiazines. Mood stabilizers like, carbamazepine/oxcarbamazepine, valproate and lamotrigine have also been reported to be associated with hyponatremia with the incidence rate with carbamazepine in the range of 4.8% to 41.5% in small sample size studies. Among the various benzodiazepines and Z-category drugs, clonazepam, lorazepam, oxazepam, triazolam, alprazolam, temazepam, clorazepate, and zolpidem have also been shown to be associated with hyponatremia in various case reports. Among the various mechanisms, Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) has been reported to be the most common mechanism responsible for psychotropic associated hyponatremia.[31] Many studies have evaluated the risk factors for development of hyponatremia with psychotropics (Table-12). Most of this literature is available in relation to antidepressants.

Table-12: Risk factors for development of hyponatremia associated with psychotropics[31,32]

1. **Demographic variables:** older age, female gender (for antidepressants)
2. **Physical characteristics:** low body weight, especially when the weight is <60 kilograms
3. Concomitant medications: diuretics, anticancer drugs, antihypertensives, antidepressants, anti-diabetics, anti-inflammatory drugs, and anti-epileptics, Cytochrome 450 inhibitors, polypharmacy
4. **Past History:** past history of hyponatremia
5. Co-morbid medical conditions: Diabetes mellitus, hypertension, hypothyroidism, Obstructive Pulmonary Disease (COPD), cardiac failure, head injury, stroke, cirrhosis of

liver, malignancies
6. **Baseline serum sodium levels:** low baseline levels (i.e., serum sodium levels <138 mmol/L)
7. **Environmental factors:** summer season
8. **Nature of Psychiatry disorder:** early onset psychiatric illnesses, longer duration of psychiatric disorder, prolonged admission
9. **Dose of psychotropic:** Inconclusive (antidepressants and antipsychotics); higher dose in case of carbamazepine
10. **Duration of treatment:** during the initial part of treatment with psychotropics

The clinical presentation of hyponatremia is influenced by the severity of hyponatremia, i.e., mild (130-134 mmol/l), moderate (125-129 mmol/l) and severe (< 125 mmol/l) hyponatremia. Often the hyponatremia is asymptomatic, but when symptomatic the patient may report of symptoms like headache, confusion, muscle cramps, lethargy and severe agitation. Patients with serum sodium level <120 mmol/l can present with symptoms like seizures, delirium, stupor, Cheyne–Stokes breathing, diminished deep tendon reflexes and coma. It is important to note that the initial manifestation of hyponatremia may be non-specific and actually the manifestation may overlap with manifestation of depression (e.g., fatigue, anorexia, confusion) or other side effects of the ongoing medications (e.g., gait disturbances, vomiting, fatigue). Hence, it is important to take a proper history and if there is worsening of these symptoms after the starting of the psychotropics, a possibility of hyponatremia should be considered.

Whenever a patient on psychotropics, especially antidepressants, reports worsening of symptoms (e.g., fatigue, anorexia, confusion) within few days of starting the medications or presents to emergency or medical ward with seizures, other neurological signs and symptoms or altered sensorium/stupor or coma, a possibility of hyponatremia should be considered. These patients need to undergo detail assessment, which include proper history taking, physical examination and appropriate investigations (Table-7 and 8). The basic purpose of detailed assessment should be establishing the diagnosis of psychotropic related hyponatremia and ruling out all other possible causes (Table-13).

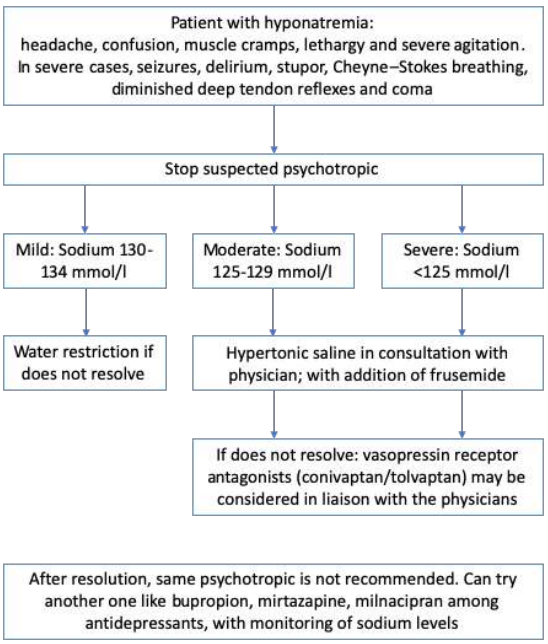
Table-13: Differential diagnosis of psychotropic associated hyponatremia

Differential Diagnosis
• Psychogenic polydipsia (especially in patients in whom antipsychotics are contributing agents)
• Other organ failure: cardiac, renal, hepatic
• Dehydration due to any cause
• Pseudo-hyponatraemia due to hyperglycaemia, hypertriglyceridemia, hypoproteinemia
• Undiagnosed physical morbidities: hypothyroidism, hypoadrenalism, SIADH due to

hormone secreting tumors, central nervous system lesions

The treatment of hyponatremia is usually guided by the severity of the hyponatremia and the clinical manifestations. Whenever a medication is suspected to be the possible cause of hyponatremia, it should be stopped immediately. If the hyponatremia is of mild severity, stopping of the offending agent may be sufficient. However, if this does not lead to improvement of serum sodium levels to the normal range, then water restriction should be considered in addition to the stoppage of offending agent(s). However, if the hyponatremia is of moderate to severe nature, then in addition to stoppage of the offending agent, patient should be given hypertonic saline, in liaison with the physician (Table-9). It is important to remember that a rapid correction of hyponatremia should be avoided, as this can lead to central pontine myelinolysis. Additionally, while using hypertonic saline infusion, furosemide should be used to prevent the kidney from concentrating urine even in the presence of high levels of Anti Diuretic Hormone (ADH). If the hyponatremia does not improve with these measures, then vasopressin receptor antagonists (conivaptan/tolvaptan) may be considered in liaison with the physicians. The management of hyponatremia due to psychotropics is presented in figure 3.

Figure 3: Management of patient with hyponatremia



Once the hyponatremia improves, rechallenge with the same agent is not recommended, if other alternative agents are available to manage the primary psychiatric illness. In fact, it is suggested that other medications from the same class should be avoided. It is suggested that if a patient has a history of hyponatremia with SSRIs/SNRIs or if the patient develops

hyponatremia with a SSRIs/SNRIs, antidepressant like bupropion, mirtazapine, milnacipran, which are considered to have lower potential to cause hyponatremia may be considered. However, for antipsychotics, current level of data does not suggest that hyponatremia with one atypical antipsychotic pose risk for development of hyponatremia with another atypical antipsychotic. Clozapine is reported to improve serum sodium levels and it is considered as an option for management of primary illness in patients who develop hyponatremia with other antipsychotics. It is recommended that the serum sodium levels should be monitored while the patient is being challenged with a newer agent.

It is of paramount importance that, the clinicians are able to identify the persons at high risk for development of hyponatremia and they take appropriate measures to prevent the same. While starting psychotropics the clinicians should be aware about the risk factors for hyponatremia and should avoid medications with higher potential to cause hyponatremia if other options are available. Further, in persons at high risk of developing hyponatremia, the clinicians should psychoeducate the patient and their family members about the clinical manifestations of hyponatremia and what should be done in such a situation. Additionally, the serum sodium should be monitored closely in these patients during the initial phase of treatment, especially when the doses of medications are being increased. The doses of the medications potentially to cause hyponatremia should be increased slowly and other medications which can cause/contribute to hyponatremia should be changed or stopped in liaison with specialist, without comprising the management of the primary illness for which this agent was being used.

Cardiac Side Effects

The cardiac side effects of psychotropics include tachycardia, bradycardia, arrhythmias, QTc prolongation, coronary artery disease/myocardial infarction, atrioventricular (AV) block, ventricular extrasystole, ventricular bigeminy, ventricular systoles, hypotension, hypertension, myocarditis, cardiomyopathy and pericarditis. Some of the antipsychotics are also known to have direct depressant effect on the heart and can lead to sudden cardiac death.[33,34] Some of the cardiac effects may be due to direct effect of the psychotropics on the heart; others may be an outcome of drug interactions or may be an outcome of use of concomitant medications, which also have similar cardiac side effects. The cardiac manifestations may also be secondary to other side effects of psychotropics, for example hyponatremia leading to arrhythmias.[33] However, it is important to remember that these side effects are not clinically significant in most of the patients, but in occasional patients these can be life-threatening and fatal. Hence, there is a need to monitor the cardiac status of the

patients on psychotropics, especially those who are at high risk for developing cardiovascular side effects (Table-14). Another issue to remember is the fact that patients with various psychiatric illnesses are also associated with higher rate of cardiac ailments and are also associated with poor outcome.[33,34] Due to all these factors, all patients considered for starting of psychotropics, especially antipsychotics, may be considered for ECG and blood pressure evaluation.[33,34]

Table-14: Patients at high-risk of developing cardiovascular side effects of psychotropics (adapted from Manolis et al, 2019)[34]

- Elderly
- Children and adolescents
- Patients with pre-existing cardiovascular risk factors or cardiac disorders, including coronary artery disease, acute coronary syndrome, myocardial infarction, heart failure
- Patients receiving concurrent medications with potential cardiac effects
- Poor Cyp450 metabolizers
- Patients with history of ventricular arrhythmias or syncope
- Family history: long QT syndrome, sudden death, diabetes mellitus, hypertension, dyslipidemia, obesity
- Polypharmacy
- Use of higher doses
- Electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia)

Among the various cardiac side effects those which have higher risk of fatality include significant QTC prolongation leading to torsade de pointes, myocarditis, cardiomyopathy and pericarditis.

QTc Prolongation and Torsade de pointes

Various psychotropics have been reported to carry varying risk of QTc prolongation and Torsade de pointes (Table-15). However, it is important to note that for some of the psychotropics, the data is not available to estimate the appropriate risk of this side effect. The risk of QTc prolongation and Torsade de pointes increases with the increase in the doses of most of the psychotropics which are considered to have higher risk. Some of the demographic and clinical factors have been reported to be associated with increased risk of QTc prolongation (Table-16). These must be kept in mind, while selecting psychotropics, and whenever possible, the medications with higher risk should be avoided, if there is an option to use medications with lower or no risk of QTc prolongation and Torsade de pointes. Psychotropic medications reported to be associated with sudden cardiac death include chlorpromazine, droperidol, haloperidol, levomepromazine, pimozide, thioridazine, cloza-

pine, olanzapine, quetiapine, ziprasidone, zotepine, pimavanserine, risperidone, sulpiride, tricyclic antidepressants (amitriptyline), SSRIs.[35]

Table-15: Risk of QTC prolongation with psychotropic medications (adapted from Wenzel-Seifert et al, 2011)[36]

High Risk	Moderate Risk	Low Risk	No Risk
Thioridazine*	Chlorpromazine*	Haloperidol*	Zuclopenthixol
Pimozide*	Risperidone	Fluphenazine	Paliperidone**
Levomepromazine	Clozapine**	Flupenthixol	Aripiprazole
Sertindole**	Sulpiride	Amisulpiride	Opipramol
Quetiapine**	Clomipramine	Zotepine	Paroxetine***
Risperidone**	Ziprasidone**	Olanzapine	Sertraline***
Amitriptyline***	Fluoxetine	Mirtazapine	Fluvoxamine
Imipramine***		Trazadone	Reboxetine
Doxepin***		Mianserin	Duloxetine
Desipramine***		Venlafaxine**	Methylphenidate***
Nortriptyline***		Citalopram***	Atomoxetine***
Maprotiline		Escitalopram	Carbamazepine
Lithium**		Bupropion	Valproate
		Methadone*	Lamotrigine
		Levomethadone*	

TdP risk according to the Arizona Arizona's Center for Education and Research on Therapeutics (Arizona CERT)
*Generally accepted elevated risk of TdP
**Rare case reports of TdP, possible but not adequately documented TdP risk
***Weak association with TdP, unlikely at therapeutic doses, elevated TdP risk in the presence of congenital QT syndrome

Table-16: Risk factors for QTc prolongation & Torsade de Pointes[33,36]

- **Female sex**
- **Elderly**
- **Congenital QT syndrome**
- **Childhood history of recurrent seizures or syncopal attacks**
- **History of dizziness, light headedness, palpitations**
- **Idiopathic long QT syndrome**
- **Electrolyte imbalance:** hypokalemia, hypomagnesaemia
- **Underlying cardiac diseases:** myocardial hypertrophy, atrioventricular block, ischemic heart, bradycardia, congestive cardiac failure
- **Substance abuse:** especially alcohol, cocaine
- **Polypharmacy:** patients taking of multiple medications each of which prolongs QTc intervals (e.g., an antipsychotic, antidepressant, and antibiotic)
- **Drug interactions which increase the dose of a medication with QTc effects**

In majority of the patients, QTc prolongation is asymptomatic, and is identified only when the ECG is being monitored. However, some of the patients may present with non-specific symptoms like light headedness, with or without palpitations, syncope or presyncope and

sudden cardiac arrest. Depending on the severity of ventricular tachyarrhythmia, the patients may also present with hypotension. On investigations, the patients may show prolonged QTc along with or without other cardiac rhythm problems. A QTc interval of 420 (±20) milliseconds is considered to be normal in a healthy person after puberty. As per the American Heart Association (AHA)/American College of Cardiology (ACC)/ Heart Rhythm Society (HRS) Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death suggests that QTc interval of >450 milliseconds for men, and >460 milliseconds for post-pubertal women are considered to be abnormal.[37]

Additionally, evaluation should include reviewing the whole prescription and looking for other medications which can prolong QTc interval (Table-17), evaluating the various serum electrolytes disturbances (i.e., looking hypokalemia, and hypomagnesemia). Magnesium sulphate can be used in patients in prolonged QTc interval, even in patients with normal serum magnesium levels.

The management of patients with prolonged QTc and torsades de pointes is usually guided by the symptoms and the hemodynamic stability. Patients, who are clinically unstable, may require use of antiarrhymic medications, and electrical cardioversion/defibrillation.

First step involves achieving hemodynamic stability by ensuring the general measures (Table-3). The patients need to be closely monitored for the cardiac functioning. Depending on the severity of the QTc prolongation, the implicated agent has to be stopped (if the QTc is > 500 milliseconds) or the dose can be reduced and ECG needs to be monitoring. If the patient has associated hypokalemia and hypomagnesemia, then these must be corrected.

Table-17: Medications that can prolong the QTc Interval[33]

Class I A Antiarrhythmic medications: disopyramide, N-acetyl procainamide, procainamide, quinidine
Class III Antiarrhythmic medications: amiodarone, bepridil, bretylium tosylate, d-sotalol, dofetilide, sotalolhydrochloride
Antibiotics: erythromycin, gatifloxacin, moxifloxacin, pentamidine, sparfloxacin, trimetoprim/sulfamethoxazole
Antimalarials: quinine, chloroquine, halofantrine hydrochloride
Calcium channel blockers: bepridil, prenylamine, terodiline
Antipsychotic medications: chlorpromazine, droperidol, haloperidol (in high doses and iv form), pimozide, thioridazine, ziprasidone
Antidepressants: All tricyclic antidepressants especially amitriptyline hydrochloride, doxepin hydrochloride, maprotiline; citalopram, lithium
Miscellaneous: amantadine, chloral hydrate, ketanserin, organophosphates (veterinary), probucol, succinylcholine chloride, tacrolimus, vasopressin

To prevent cardiac arrest and development of prolonged QTc and torsade de pointes, it is important to do baseline ECG and monitoring the ECG and serum potassium levels. While using medications which have higher risk of QTc prolongation, the doses should be increased slowly. The patient needs to be psychoeducated to report immediately, if they have new symptoms in the form of palpitation, lightheadedness, syncope, etc. In patients at high risk of cardiovascular side effects it is better to avoid medications that have high risk of QTc prolongation.[33,34]

Hypotension: Many psychotropics are known to cause hypotension, especially the orthostatic hypotension. Different authors have categorised the risk in different manner. A review of product descriptions reported variable risk with different psychotropics (Table-18).[38] The risk of hypotension is further increased when antipsychotics are combined with various antihypertensive medications, and other cardiac medications like angiotensin II receptor blocker, nitrates, calcium channel blockers, diuretics, α-adrenergic blockers, etc. Additionally, the risk of orthostatic hypotension increases in patients with various diseases associated with autonomic failure (i.e., diabetesmellitus, alcohol dependence, Parkinson's disease, multiple system atrophy, and pure autonomic failure) or presence of dehydration.[39] The clinical manifestation of orthostatic hypotension can include dizziness, light-headedness, headache, visual disturbance and generalized weakness. If these symptoms are not given due importance, orthostatic hypotension can lead to syncope (which can lead to further complications like, fractures and haemorrhage), transient ischaemic attack, stroke, myocardial infarction and death.[39]

Table-18: Risk of hypotension[38]

Very often (10% or more)	**Often (1 to < 10%)**	**Occasional (0.1 to <1%)**	**Rarely/Very rarely (<0.1%)**
Amitriptyline	Citalopram	Citalopram	Bupropion
Tranylcypromine	Imipramine	Doxepine	Trazadone
Trimipramine	Maprotiline	Duloxetine	Ziprasidone
Chlorprothixene	Mirtazapine	Fluoxetine	Carbamazepine
Flupentixol	Moclobemide	Fluvoxamine	Diazepam
Levomepromazine	Nortriptyline	Mianserin	Flurazepam
Olanzapine	Reboxetine	Milnacipran	Hydroxyzine
	Trazadone	Mirtazapine	Nitrazepam
	Venlafaxine	Paroxetine	Opipramol
	Modafinil	Sertraline	Levomethadone
	Amisulpride	Venlafaxine	Methadone
	Clozapine	Atomoxetine	
	Fluphenazine	Modafinil	
	Haloperidol	Aripiprazole	

	Olanzapine Paliperidone Quetiapine Sertindole Thioridazine Zuclopenthixol Opipramol Buprenorphine	Asenapine Paliperidone Quetiapine Risperidone Sertindole Sulpiride Ziprasidone Carbamazepine Buspirone Diazepam Lorazepam Oxazepam Pregabalin Galantamine Rivastigmine Buprenorphine+Naloxone Methadone Naltrexone	

The assessment of orthostatic hypotension includes recording of blood pressure appropriately. To consider that a person has orthostatic hypotension, there should be minimum fall of 20 mm of Hg systolic blood pressure or 10 mm of Hg of diastolic blood pressure within 2-5 minutes of standing from siting position. The assessment should involve looking for other possible medications and physical health conditions which could be contributing to the postural fall. The management of orthostatic hypotension is influenced by the severity of the symptoms and the associated complications. If the symptoms are not severe, then initially the dose of the offending psychotropic agent can be reduced and the blood pressure can be monitored. Additionally, the patients can be advised to use abdominal binders (starting from morning before getting up and removed at the bedtime) or leg compression stockings, and increase the fluid intake (1.25 to 2.5 L/day). However, if the symptoms are severe and disabling then the offending agent has to be stopped.[39]

While using psychotropics that are associated with higher risk of postural hypotension, all the patients should be advised to avoid sudden change in the posture, especially while getting up from the bed in the morning.[39]

Additionally, they should be informed that they should avoid physical activity, intake of alcohol, carbohydrate rich food, and exposure to heat. They can be advised to use abdominal binders (starting from morning before getting up and removed at the bedtime).

Hypertension: Some of the psychotropics are also known to be associated with development of hypertension. The review which included the product descriptions of various psychotropic agents reported highest incidence of hypertension with atomoxetine (Table-19).[38] The rise in

blood pressure could be an outcome of direct effect of the ongoing psychotropics or may be an outcome of the ongoing concomitant medications.[40] Hence, at the time of starting of various psychotropics that are associated with development of hypertension, it is advisable to assess the blood pressure at the baseline.

Patients with raised blood pressure may manifest with headaches especially in the early morning, bleeding from nose, visual disturbances, and buzzing in the ears. Patients with severe hypertension may additionally present with nausea, vomiting, anxiety, chest pain, and fatigue and confusion. However, in majority of the patients, high blood pressure is asymptomatic and is detected only on routine screening. Undetected high blood pressure may lead to angina, myocardial infarction, congestive cardiac failure, arrhythmias, sudden cardiac death and renal failure.

Whenever, rise in blood pressure is suspected, multiple readings must be recorded to confirm the presence of high blood pressure. Additionally, efforts must be made to identify any other cause or contributing factor for hypertension. Whenever a patient on psychotropics presents with new onset hypertension, the role of the psychotropic should also be considered. Whenever a psychotropic is suspected to be the offending agent, it should be stopped and blood pressure should be monitored.

Table-19: Risk of hypertension[38]

Very often (10% or more)	**Often (1 to < 10%)**	**Occasional (0.1 to <1%)**	**Rarely/Very rarely (<0.1%)**
Atomoxetine	Bupropion Citalopram Duloxetine Milnacipran Reboxetine Tranylcypromine Venlafaxine Methylphenidate Clozapine Paliperidone Risperidone Galantamine Memantine Rivastigmine Buprenorphine+Naloxone combination	Amitriptyline Citalopram Duloxetine Maprotiline Nortriptyline Paroxetine Sertraline Trazadone Bupropion Modafinil Sulpiride Risperidone Ziprasidone Carbamazepine Buspirone Pregabalin Naltrexone Varenicline	Duloxetine Carbamazepine Ziprasidone

Myocarditis

Myocarditis is a rare side effect of antipsychotics, most commonly reported with use of clozapine. It is characterised by inflammation of the myocardium. Besides clozapine, myocarditis has also been reported with use of quetiapine,[41] haloperidol and chlorpromazine,[42] amisulpiride, aripiprazole, asenapine, olanzapine, quetiapine, and risperidone. The reported incidence for myocarditis with clozapine is 0.015–8.5%, and that for olanzapine is 0.002%, risperidone is 0.002% and that for quetiapine is 0.006%.[14,43–45] In terms of geographical variation, higher incidence of clozapine associated myocarditis has been reported in people from Australia.[14,44,45]

Clozapine associated myocarditis has maximum level of evidence and it is suggested to be due to immunoglobulin E (IgE)–mediated hypersensitivity reaction.[44] It is usually seen during the initial part of the treatment (first 2-3 months) with clozapine in previously healthy adults, with some cases reported as late as 1 year.[14,44,45] The dose range associated with myocarditis has varied from 50 to 600 mg/day with a median dose of 250mg/day.[14,44,45] Various risk factors associated with clozapine associated myocarditis include rapid increase in dose, increasing age, concomitant use of sodium valproate, SSRIs, lithium, another second generation antipsychotic, obesity, higher body-mass index, and increased serum concentration of creatine kinase.[14,44,45]

The clinical presentation of myocarditis could be variable and it may manifest with non-specific symptoms like fever, flu like symptoms, nausea and dizziness. Some of the patients may present with cardiac symptoms in the form of tachycardia, tachypnea, chest discomfort, and hypotension. The detailed examination may additionally reveal presence of crepitations, additional heart sounds with gallop rhythm, pericardial rub, and raised jugular pressure. Some of the authors have proposed diagnostic criteria for clozapine associated myocarditis. According to one of the criteria either the patient should have histopathological evidence on of myocarditis on myocardial biopsy within 45 days of starting of clozapine or should have evidence of new signs of cardiac dysfunction (HR >100 bpm for 24 hours, third heart sound, basal crepitations, peripheral edema) with or without fever along with presence of at least 1 of the following abnormalities: elevated Troponins T and I [> 2 times of upper limit of normal], ECG changes suggestive of myocarditis, evidence of heart failure on X-ray, elevated Creatine kinase-MB (CK-MB) [> 2 times of upper limit of normal], radiographic evidence or left or right ventricular systolic dysfunction, MRI confirming myocarditis and ruling out other causes of myocarditis.

Investigations in a patient suspected to have myocarditis should include haemogram (may show evidence of eosinophilia), and other inflammatory markers, i.e., C-reactive protein (CRP), troponin T and I, creatine kinase-MB (CK-MB), B-type natriuretic peptide (BNP), N-terminal fragment of pro-BNP (NT-pro-BNP), interleukin-6 (IL-6) (inconsistently reported), and tumor necrosis factor-α (TNF-α) (inconsistently reported), all of which may be increased. Additionally, the patient may have nonspecific ECG abnormalities or arrhythmias. Other

investigations should include transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (CMRI). The TTE may reveal regional or global left ventricular dysfunction with normal wall thickness, or the patient may show biventricular systolic dysfunction with normal wall thickness. CMRI can provide similar information as TTE, and additionally may provide evidence for scar and oedema (inflammation) within the myocardial tissues and is considered to be more sensitive and specific for diagnosis of myocarditis.[14,44,45] CMRI is considered to be most useful for diagnosing clozapine associated myocarditis. It is important to remember that endomyocardial biopsy (EMB) is considered to be gold standard diagnostic tool for myocarditis, which may reveal evidence of eosinophilic inclusions and inflammatory cellular infiltrates with or without associated myocyte necrosis. However, it is usually not recommended in view of invasiveness.[14]

As the drug induced myocarditis is a medical emergency, management involves immediate stoppage of the offending agent, and general measures (Table-4). Specific treatments are instituted based on the severity of the cardiac symptoms and include corticosteroids, diuretics, beta-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. All of these must be used under the supervision of a cardiologist or a physician. Among all these, beta-adrenergic blockers are known to improve the ventricular function, reduce progression of cardiac failure, and increase chance of survival.[14,44,45]

As clozapine is associated with myocarditis, in terms of prevention, it is recommended to carryout baseline thorough cardiac evaluation and investigations and monitor the same regularly (Table-9) for first 4 weeks to detect myocarditis at an early stage. The monitoring may be increased if the person manifests signs and symptoms suggestive of myocarditis, either on physical examination (i.e., pulse rate more than 120 bpm or an increase in heart rate by more than 30 bpm) or on investigations (rise in CRP levels of 50-100 mg/l or rise in Troponin levels < twice the upper limit of normal). Generally, it is recommended that clozapine must be discontinued if the troponin levels increase more than the twice the upper limit of normal or CRP levels rise more than 100 mg/L.[14]

Cardiomyopathy

Cardiomyopathy involves structural abnormality of the left ventricle and has been reported with the use of clozapine, aripiprazole, olanzapine, quetiapine and risperidone.[43] The reported incidence with various antipsychotics varies from 0.04 to 0.2%.[43] Maximum level evidence is available for clozapine and as with myocarditis the incidence rates are higher for people from Australia. A retrospective study estimated the incidence of cardiomyopathy to be 4.65 % (6/129) in patients receiving clozapine and followed up for 11 years (0.42 %/year.[46] Compared to myocarditis, cardiomyopathy is usually seen by 6-9 month of starting of clozapine, however, it is important to note that it can occur as early as 1 month and as late as 6 years.[44,47]

In terms of clinical manifestations, cardiomyopathy associated with antipsychotics is mostly asymptomatic and most of the patients also do not have a previous history of cardiac ailment and any potential medical risk factors.[44,47] Among the various risk factors, low ejection fraction is considered to be a risk factor for development of cardiomyopathy.

If symptomatic, the clinical features of cardiomyopathy may include breathlessness (most common symptom), poor/decreased exercise tolerance, orthopnoea, paroxysmal nocturnal dyspnoea, tachycardia, palpitation, chest pain, and fatigue. Physical examination may reveal evidence of peripheral oedema which may be increasing overtime, raised jugular venous pressure, systolic murmurs (due to mitral &/or tricuspid insufficiency), and coarse crackles at the base of the lungs.

Diagnosis is usually based on presence of left ventricular insufficiency (ejection fraction < 50 % of normal) in the echocardiography. TTE may reveal dilated and thin-walled LV with systolic impairment. Other supportive evidence in favour of diagnosis includes nonspecific ECG changes (Q waves seen in myocardial infarction, left ventricular hypertrophy and strain seen in hypertension etc.), increased serum concentrations of BNP and N-terminal pro 'b' type natriuretic peptide (NT-proBNP). Cardiac MRI can be useful in distinguishing between other common causes of cardiomyopathy and can help in determining the prognosis.

Management involves stopping of the offending agent and taking care of general measures (Table-4). This may be sufficient in improvement in the cardiac function, in patients with ejection fraction >25% at the time of diagnosis. Some of the patients may require supportive measures in the form of diuretics, beta-blockers, and ACE inhibitors, in liaison with a cardiologist.[44,47]

Pericarditis

Pericarditis as a side effect of antipsychotics has been linked with the use of clozapine and quetiapine.[48,49] It is documented as early as 7 days and as late as 7 years after starting of clozapine[49] and long-term use of quetiapine.[48] Some case reports suggest development of constrictive pericarditis.[48] The clinical presentation of pericarditis includes present mild flu-like symptoms, fever, tachycardia, gastrointestinal symptoms, chest pain, shortness of breath and dyspnea. Investigation in patients suspected to have pericarditis should include ECG, creatine phosphokinase-MB levels, CRP levels, Troponin levels, and echocardiography. Patients with pericarditis can show increased Troponin I and/or T levels, eosinophilia, increased BNP and pro-BNP levels. Management involves discontinuation of the offending agent and addressing the cardiac decompensation.[49]

Hyperammonemic Encephalopathy

Hyperammonemia (blood ammonia levels >45μmol/L) is a potentially life-threatening condition, that has been reported to be associated with valproate/valproic acid, topiramate, lamotrigine, zonisamide, carbamazepine, phenytoin, risperidone and olanzapine.[6,50–52] The drug most commonly implicated for hyperammonemic encephalopathy is valproate. The risk

factors for valproate associated hyperammonemic encephalopathy include urea cycle disorder, immature hepatic function, hereditary or dietary-induced carnitine deficiency, comorbid diseases (thyroid dysfunction), increased protein load, polypharmacy with more than one agent (concomitant use of other antiepileptics), and poor nutrition.[5,6] Available data suggest that the valproate associated hyperammonemic encephalopathy is not related to dose of valproate and duration of use of valproate.[5]

The clinical features of valproate associated hyperammonemic encephalopathy can include nonspecific symptoms, or in the form of gastrointestinal symptoms, neurological symptoms, behavioural symptoms, sleep related issues, and altered mental state examination and coma (Table 7 and 8).[5,6]

The diagnosis of valproate/medication associated hyperammonemic encephalopathy is usually based on ruling out the other possible causes of the clinical presentation, establishing high ammonia levels and ruling out other possible causes of hyperammonemic encephalopathy. Patients with hyperammonemic encephalopathy have normal liver function test results.[5,6]

Besides the routine investigations, if a patient is suspected to have hyperammonemic encephalopathy, serum ammonia levels must be done. Other investigations can include neuroimaging of brain, investigations for evaluating the defects in urea cycle, serum glutamate levels and serum carnitine levels (Table-8).[5,6]

Management involves stopping the offending agent, improving the hydration, restricting the intake of the proteins, monitoring of serum glucose levels, and use of agents like lactulose/ rifaximin/neomycin. Some of the authors recommend the use of L-carnitine. Patients with severe hyperammonemic encephalopathy may require the use of furosemide, acetaglutamide, and mannitol to reduce cerebral edema. If the patient is found to have deficiency of N-acetylglutamate (NAG) synthetase than N-carbamylglutamate (NCG) may be used. Dialysis is recommended if the serum ammonia level is between 300-500 μmol/L (Table-9). [5,6]

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a rare side effect of SGAs, which is mostly reported in the form of case reports/case series. DKA has been reported with the use of clozapine, olanzapine, risperidone, quetiapine, and aripiprazole. Most commonly associated antipsychotics include olanzapine and clozapine. Some of the reports suggest associated of DKA with use of polypharmacy (i.e., use of more than one antipsychotic agent, with one of the medication being a SGAs). It is usually seen in initial phase of treatment with the particular antipsychotic, with majority of cases seen during the initial 6 months of starting treatment. The risk factors for development of DKA with antipsychotics although reported inconsistently include middle age, male gender, unrecognised hyperglycemia or raised HbA1c levels, being overweight, and weight gain with the use of antipsychotic used.[13,53] However, a nationwide nested case control study reported a diagnosis of type-2 diabetes

mellitus to be the only risk factor.[54] DKA may also be seen secondary to acute pancreatitis caused by various psychotropics like valproate[55] and antidepressants.[56] The clinical presentation of diabetic ketoacidosis includes history of recent weight gain or weight loss, polyuria, polydipsia and polyphagia preceding the acute presentation. The acute presentation may include weakness, fruity breath, nausea, vomiting with coffee-ground content, dehydration and altered sensorium.[53]

The investigations specific for DKA include HbA1c, estimation of urine and serum ketone bodies, assessing the effective serum osmolality (mOsm/kg) and anion gap (mEq/L). Management includes maintaining hydration, addressing the disturbances in the serum electrolyte levels, administration of insulin to normalize the serum glucose levels with 5-7 point monitoring (Table-9).

Psychotropics and Pneumonia

In the recent years there is a considerable data to suggest the association of psychotropics, especially antipsychotics with development of aspiration. The available data suggests that the risk ratio of developing aspiration pneumonia with antipsychotics is much higher, when compared to those not on antipsychotics. A recent metanalysis of the data from 14 studies suggests that the risk ratio of development of pneumonia is 1.69 (95% CI: 1.34-2.15) with the first-generation antipsychotics and that for SGAs is 1.93 (95% CI: 1.55-2.41), when compared to no antipsychotics.[57] The studies which have compared the first generation and SGAs suggest lack of significant difference between the two groups of antipsychotics.[57] The antipsychotics which have been commonly associated with the development of aspiration pneumonia include clozapine, risperidone, quetiapine, olanzapine, zotepine and haloperidol.[57–59] Although there is lack of consensus, but there is some data to suggest that aspiration pneumonia associated with use of antipsychotics is associated with increased mortality among the elderly.[60] The various risk factors for development of aspiration pneumonia include older age, male sex (recurrent pneumonia reported to be more common in females in one study), dementia, presence of chronic respiratory diseases like asthma and chronic obstructive pulmonary disease, tuberculosis within 1 year before baseline, dysphagia, smoking, cerebrovascular disease, polypharmacy (i.e., combined use of clozapine and another antipsychotic), concomitant use of benzodiazepines, valproic acid, systemic corticosteroids, and the early phase of treatment (with clozapine).[57,61–63] There is inconsistent association of aspiration pneumonia with doses of antipsychotics, with some studies reporting clozapine to have a clear association with development of recurrent aspiration pneumonia in a dose-dependent manner,[61] whereas other studies reporting no association of clozapine doses with risk of development of aspiration pneumonia.[63]

The increase risk of aspiration pneumonia with antipsychotics has also been seen in patients with bipolar disorder, and it has been reported to be dose related, with higher doses of antipsychotics associated with higher risk of aspiration pneumonia.[64] Interestingly one of the

studies which involved patients with bipolar disorder reported lithium to have a protective effect.[64]

Besides antipsychotics, benzodiazepines and benzodiazepine-related drugs (BZRD) like zopiclone and zolpidem have also been shown to be associated with increased risk of aspiration pneumonia due to sedation, especially in elderly with dementia.[65,66] There is some data to suggest increased risk of pneumonia with antidepressants, valproate, carbamazepine and pregabalin too, especially among the elderly.[66]

The risk factors for development of aspiration pneumonia reported in the literature include older age, being underweight, and smoking habit.[67] It is also important to note that available literature in the general population suggests association of aspiration pneumonia and/or community acquired pneumonia with the use of alcohol, medication overdoses, seizures, stroke, head injury, oesophageal conditions, neurological conditions like Parkinson's Disease, myasthenia gravis etc, protracted vomiting and lying in prolonged recumbent position, malnutrition, past history of community acquired pneumonia, bronchial asthma, chronic bronchitis/chronic obstructive pulmonary disease, poor level of functioning, poor dental hygiene, use of immunosuppressive agents including oral steroids, and use of proton pump blockers.[68] These factors also must be taken into account while psychoeducating the patient and the family for prevention of aspiration pneumonia in patients on psychotropics (Table-9).

The clinical picture of aspiration pneumonia is usually influenced by the severity of illness and the patient may present with mild respiratory symptoms (like cough with or without expectoration, difficulty in breathing, fever, fatigue, nausea, vomiting, diarrhoea, fatigue, etc) to the outpatient services or may land up in medical emergency or ward with severe symptoms like respiratory failure and septic shock. On examination, the findings may include clinical features fever or hypothermia, tachycardia, tachypnea, dullness to chest percussion in the areas of consolidation, pleural rub, hypotension, altered sensorium or delirium.[69] It is important to remember that the clinical presentation may have some overlap with other medical emergencies reported to be associated with use of psychotropics. Hence, all these should be considered as differential diagnosis. Additionally, other causes of pneumonia must be ruled out, before considering the possibility of psychotropic associated aspiration pneumonia.

Diagnosis of aspiration pneumonia is based on the physical examination findings and the findings in the chest X-ray. Other investigations in patients with aspiration pneumonia are guided by the severity of symptoms, establishing the causative agent and differential diagnosis (Table-8).

As with other conditions, offending agent should be immediately stopped. Depending on the severity of the symptoms, patient need to be admitted and the general measures (Table-4) need to be instituted. The selection of appropriate antibiotics must be done in liaison with the

specialist. The supportive measures should include the oxygen support, maintaining an intravenous assess and fluids as per the requirement, monitoring of the cardiac parameters and maintaining hydration (Table-9).

Upper Gastrointestinal Bleeding

Antidepressants, especially SSRIs have been linked to increased risk of bleeding. The various sites of bleeding reported in the literature include ecchymosis, bleeding gums, sub-conjuctival bleeding, bleeding into joints, epistaxis, intracranial bleeding, increased vaginal bleeding, postpartum haemorrhage, epidural hematoma, upper gastrointestinal bleeding (UGIB), and increased risk of perioperative bleeding.[70] However, the bleeding which has received significant clinical attention is UGIB. A metanalysis, which included 22 studies, of which 16 were case-control studies and 6 were cohort studies, with total sample size of more than 1,073,000 individuals, reported the odds ratio of UGIB with SSRIs to be 1.55 [95% confidence interval (CI):1.35–1.78], compared to those not receiving SSRIs.[71] Another metanalysis which included data of 1,255,073 participants (106,629 cases and 1,148,444 controls), from 31 case-control studies and 11 cohort studies reported the odd ratio for increased risk of UGIB with SSRIs to be 1.41 (95% CI 1.27–1.57) in the case control studies and 1.36 (95% CI 1.12–1.64) in the cohort studies.[72] Besides SSRIs, other antidepressants which have been linked to increased risk of UGIB include mirtazapine, and bupropion. A metanalysis showed the risk of UGIB with mirtazapine to be 1.17 [95% confidence interval (CI): 1.01-1.38], with no significant difference in the risk between SSRIs and mirtazapine or SSRIs and bupropion.[73]

In terms of risk factors for UGIB, the most consistently reported risk factors include concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents (like aspirin, and clopidogrel), and use of both NSAIDs and antiplatelet drugs. Further the data suggest the risk is higher during the initial phase of therapy. The concomitant use of acid suppressive agents reduces the risk of UGIB.[71] A case series analysis that included data from 7 population-based health care databases and data of 114,835 patients with UGIB with information of 930,888 person-years of follow-up reported that the relative risk of UGIB was 2.06 (95% CI: 1.94-2.18) with SSRI monotherapy, 4.60 (95% CI: 4.09-5.17) with combination of SSRIs and low-dose aspirin, and 6.95 (95% CI: 5.97-8.08) with a combination of SSRIs and NSAIDs.[74] Increased risk of UGIB with concomitant use of warfarin has also been reported.[75] In terms of Number needed to harm (NNH), some of the authors have estimated that for one patient to develop UGIB with SSRIs, 791 patients need to be exposed to SSRIs. However, when the SSRIs are combined with NSAIDs and antiplatelet agents the NNH reduces to 160 and 294 per year respectively.[71] In terms of duration of exposure to SSRIs, although there is lack of consensus, but some of the studies have reported highest risk during the first one month of exposure to SSRIs, whereas others suggest the risk persists throughout the duration of exposure to SSRIs .[70] Other risk factors which have been

reported to be associated with higher risk of UGIB with SSRIs include age more than 80 years and past history of UGIB.[76]

Hematemesis can be an acute medical emergency associated with the use of antidepressants, especially SSRIs. Assessment of a patient on SSRIs who presents with hematemesis, should involve assessment for risk factors and ruling out other possible causes of UGIB which could be peptic ulcer and/or malignancy, besides other causes. The offending agent(s), should be stopped and if the patient is on concomitant medications, same should be stopped in liaison with other specialists. Management involves acute stabilization of haemodynamic status, and evaluating for the need for blood transfusion. Once patient has stabilized haemodynamically, endoscopy should be considered to evaluate for other possible causes of hematemesis and addressing the same.

In patients who require further continuation of antidepressants, which are considered to be less likely to cause UGIB should be considered and concomitant use of proton pump blockers should be considered. The agents with lower risk for bleedings include tianeptin, reboxetine, SNRIs and tricyclic antidepressants.

Severe Intestinal Obstruction

Constipation is a common side effect of many psychotropic agents. However, some of the psychotropics can lead to severe gut hypomotility, manifesting as paralytic ileus, faecal impaction, bowel obstruction, necrotizing colitis, and intestine/bowel perforations.[77–79] Among the various psychotropics, antipsychotics have been most commonly reported to be associated with paralytic ileus. The antipsychotics associated with paralytic ileus include clozapine, quetiapine, olanzapine, and high potency antipsychotics.[80,81] Additionally, paralytic ileus is reported to be associated with the use of anticholinergic medications and tricyclic antidepressants.[80] The risk factors for paralytic ileus include older age, female gender, higher daily dose of medication (clozapine), and concomitant use of opioids.[80] Among all the antipsychotics, gut hypomotility with clozapine has received significant research attention and this has been attributed to the anti-muscarinic effects, anti-adrenergic effects, and anti-serotonergic effects of clozapine. Additional factors which contribute to development clozapine associated gut hypomotility and paralytic ileus include cessation of smoking, delayed symptom reporting by the patients and failure on part of the clinicians to screen patients for their bowel habits.[78,82] Clozapine induced gut hypomotility has been shown to be associated with older age, male gender, first 4 months of clozapine therapy, concomitant use of other medications which can cause constipation, higher doses and past history of clozapine induced gut hypomotility.[78]

The clinical presentation of paralytic ileus and other severe gut manifestations may include pain abdomen, vomiting, and constipation. On examination patient may be found to be in acute distress with abdominal distension, haemodynamic instability (tachycardia, hypotension, tachypnea), fever, abdominal tenderness and reduced or absent bowel

movements. In severe cases, patient may present with clinical picture suggestive of septic shock.[78,79] Whenever, paralytic ileus is suspected abdominal X-ray and/or ultrasound abdomen needs to be done, which can provide clues for the diagnosis. Management is usually supportive. Stopping of the offending agent may be sufficient in many cases to relieve the ileus. However, if a patient develops perforation peritonitis, then laparotomy may be required. Usually, rechallenge with the same agent is not done in patients with paralytic ileus. Amisulpiride and aripiprazole were not been found to be associated with paralytic ileus in one of the studies. [80] In view of the high frequency of intestinal hypomotility, it is suggested that constipation in patients being considered for clozapine should be addressed before starting clozapine and other preventive measures like monitoring of bowel habits, consumption of high fibre diet and adequate fluid intake must be encouraged. Smoking should also be stopped prior to starting of clozapine.[78] When the patient on medications which can potentially cause gastrointestinal hypomotility, bowel habits must be monitored by clinicians during all the follow-up visits and appropriate preventive measures must be ensured.

Hepatic Injury

Drug induced liver injury (DILI) has been reported with some of the psychotropic medications. The mechanisms reported for development of DILI with psychotropics are broadly understood in three forms: cholestasis (for example, chlorpromazine), direct hepatocellular injury (immunologically mediated or idiosyncratic metabolic damage) or a combination of both. It is suggested than 90% of the DILI is in the form of direct hepatocellular injury. Most of the DILIs are idiosyncratic, unpredictable and not related to the dose of the medication.[83]

Further, psychotropics can also lead to indirect liver injury by increasing the risk of non-alcohol fatty liver disease (NAFLD). The medications implicated for NAFLD include antipsychotics which increase the risk or prevalence of metabolic syndrome. The most commonly implicated agents for this include olanzapine and clozapine. Clozapine has also been linked to development of acute liver injury.[83]

Direct liver injury has been reported with the use of olanzapine, clozapine, risperidone, quetiapine and ziprasidone. This usually manifest during the initial part of the treatment. The hepatic injury caused by chlorpromazine manifest in the form of acute cholestasis. Among the antidepressants, DILI has been reported with the use of imipramine, amitriptyline, Clomipramine, moclobamide, phenalzine, tianeptiine, duloxetine, venlafaxine, sertraline, fluoxetine, paroxetine, citalopram/escitalopram, fluvoxamine, trazadone, nefazodone, bupropion, agomelatine, and mirtazapine.[83] According to one of the classifications imipramine, amitriptyline, nefazodone, venlafaxine, duloxetine, sertraline, bupropion, trazadone and agomelatine are considered to have high risk of DILI.[84,85] Antidepressant

associated DILI is usually of hepatocellular pattern, with some of the molecules associated with cholestatic or mixed pattern of injury.[85]

Among the mood stabilizers, DILI has been reported to occur with carbamazepine, valproate, lamotrigine, topiramate, gabapentin and pregabalin. Very rarely, DILI has also been reported with the use of lithium. The benzodiazepines associated with DILI include diazepam, chlordiazepoxide, and flurazepam.[83]

It is also important to remember that other side effects of the same medication, for example constipation and excessive sedation can also aggravate hepatic impairment.

The clinical manifestations of DILI are usually asymptomatic or may manifest with non-specific symptoms such as fatigue, loss of appetite, and epigastric discomfort and pain over the liver area. Patients with cholestasis manifest with itching, yellowing of skin and itching over the whole body. Other clinical features may include fever, rash, and arthralgia (Table-7). It could also be indicated by increase in the serum levels alanine aminotransferase (ALT) (3 times more than the usual), aspartate aminotransferase, alkaline phosphatase (ALP) (2 times more than the usual), gamma glutamate transferase and raised serum bilirubin levels (>2mg/dL). Other investigation findings may include increase in the eosinophil count. The DILI, which is an outcome of hypersensitive reaction and is immunologically mediated is characterised by fever, rash, increased eosinophil count, and presence of auto-antibodies. It is usually seen within 1-6 weeks of starting of the implicating agent. In contrast the idiosyncratic DILI is characterised by absence of features of hypersensitivity reaction and it usually occurs after the longer latency period of starting of the offending agent. Chronic DILI manifests either as chronic hepatitis, liver fibrosis and compensated or decompensated cirrhosis, autoimmune-like hepatitis, chronic cholestasis, and vanishing bile duct syndrome.

A combination of raised serum bilirubin levels, reduced serum albumin levels and increased prothrombin time (international normalized ratio of ≥ 1.5), without any increase or a small increase in the aspartate aminotransferase levels indicate severe liver injury. Ultrasound of liver may not provide much information in acute liver injury except for mild swelling (Table-8). The patients with chronic DILI may have features of cirrhosis of liver, splenomegaly and increase in the diameters of the portal vein.

While considering DILI, other differential diagnosis, such as overdose with other medications such as acetaminophen, use of other medications which can cause DILI, over the counter medications, use of herbal preparations, exposure to hepatotoxins, viral hepatitis, autoimmune hepatitis, malignancy (primary or secondary's in the liver due to other malignancies), other liver diseases such as Wilson's disease, and vascular diseases such as Budd-Chiari syndrome and liver problems associated with congenital diseases must be ruled out.

Management of DILI is guided by the severity of the injury and the clinical manifestations. Stopping of offending agent and institution of general measures (Table-4) is the first step in

the management. Depending on the need, liver-protecting treatment should be initiated. As most of the DILI is mild (raised alanine transaminase [ALT], no significant increase in bilirubin levels and no prolongation of prothrombin time) in nature, stopping of offending agent is often sufficient. However severe DILI (raised ALT, significant increase in bilirubin levels, prolonged of prothrombin time, jaundice and liver failure) will additionally require the use of hepato-protective agents.

As majority of the psychotropics are metabolized through the liver, it is important to understand the safety of psychotropics in patients with liver diseases, especially among those who already have DILI. Once the patient develops DILI, while choosing psychotropics, the clinicians should remember to avoid medications that have extensive first pass metabolism (for example, venlafaxine, sertraline, bupropion, chlorpromazine, quetiapine) are highly plasma protein bound (all psychotropics with the exception of venlafaxine, lithium, topiramate, gabapentin, pregabalin, memantine) and medications that depend on the phase-I hepatic metabolic reactions (almost all psychotropics except lithium, gabapentin, topiramate, amisulpride, oxazepam, temazepam, lorazepam).[83] For management of primary illness, antipsychotics that are less metabolized through the liver, for example, amisulpiride and paliperidone should be considered. However, it is important to remember that, if conclusive evidence cannot be reached for the association of the liver injury and the ongoing antipsychotic medication than the antipsychotic medication can be continued with the monitoring of the laboratory parameters.[86]

Pancreatitis

Pancreatitis has been reported to be a rare side effect of antidepressants, antipsychotics and mood stabilizers. Among the various antidepressants pancreatitis has been reported with SSRIs. A metanalysis which included data of 13898 patients with type-2 diabetes mellitus and 284131 controls from nine studies and 17548 patients with acute pancreatitis and 108108 controls from four studies estimated the adjusted odds ratio to be 1.26 (95% CI: 1.13-1.40), with higher risk during the initial 2 weeks of therapy.[87] Among the other psychotropic agents, pancreatitis has been reported with the use of clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone and valproate/valproic acid.[9,88]

Badalov et al (2007)[89] gave a classification of drug induced pancreatitis and categorised the drug induced pancreatitis to 4 classes. Class-I drugs include those medications for which there is at least 1 case report in which recurrence has been documented on rechallenge. Class-II includes medications for which consistent latency (defined as time from initiation of medication to the development of disease) in 75% or more of the reported cases have been documents. Class-III includes medications for which 2 or case reports have been documented, but there is no information about rechallenge and a consistent latency period. Class-IV includes medications for which only 1 case report has been published. Most of the psychotropics are categorised in Class-III.[9]

The risk factors for antipsychotic associated pancreatitis include use of alcohol, presence of diabetes mellitus, history of cholelithiasis, and polypharmacy with concomitant use of other drugs which are linked to development of pancreatitis.[88] Majority of the patients with acute pancreatitis present with acute abdomen. Assessment of a patient suspected to have acute pancreatitis should include confirmation of diagnosis (by ruling out other possible causes of acute abdomen), ascertainment of cause of pancreatitis and ruling out other causes of pancreatitis. The history should focus on obtaining the information about other medication intake, comorbid physical illnesses (triglyceridemia, diabetes mellitus, and hypocalcemia), and comorbid substance use. Investigation panel must include ascertainment of serum amylase and lipase levels, and ultrasound of abdomen. Other investigations are guided by the differential diagnosis and severity of the pancreatitis (Table-8). Management involves stoppage of the offending agent(s), achieving the haemodynamic stability, use of antibiotics, and preventing secondary complications. Rarely, patients with severe pancreatitis may require surgical intervention (Table-9).

Once patient is clinically stabilized, alternative psychotropics must be considered to manage the underlying psychiatric disorder. There is lack of sufficient evidence for rechallenge with the same agent in patients who develop pancreatitis with a particular psychotropic agent. Hence, a rechallenge should not be considered, if other options are available.

Priapism

Priapism is a rare side effect of psychotropics, which can present as a medical-surgical emergency. It is associated with the use of antipsychotics and antidepressants like trazadone. In fact, some of the existing literature implicates antipsychotic medications as one of the common causes of drug induced priapism.[10] The commonly implicated antipsychotics include phenothiazines (chlorpromazine, thioridazine, fluphenazine, perphenazine, mesoridazine, and thiothixine), haloperidol, zuclopenthixol, molindone, risperidone, ziprasidone, olanzapine, quetiapine, aripiprazole, and clozapine.[10,90] The antidepressants commonly associated with priapism include trazadone, nefazodone, bupropion, citalopram, fluoxetine, sertraline, paroxetine and venlafaxine.[90] Other psychotropics which have been shown to be associated with priapism include buspirone, hydroxyzine. It can occur anytime during the course of use of antipsychotic agent, i.e., during the initial course of treatment, during the long-term use of antipsychotics or after the change in the dose of the antipsychotic medication.[90] Priapism is usually attributed to the alpha-adrenergic blocking properties of the psychotropic, with agents having higher potential, associated with higher risk of developing priapism.[10] It is reported both in men and women (in the form of clitoral priapism).[10] Clitoral priapism has been reported with the use of trazadone, nefazodone, citalopram, bupropion, olanzapine. Antipsychotic induced priapism is usually understood as an ischemic priapism. Some of the risk factors associated with psychotropic associated priapism reported in the literature include history of prolonged and painful erections, diabetes

mellitus, polypharmacy (either another antipsychotic) especially with agents having high alpha-adrenergic blocking properties, antidepressant (with alpha-adrenergic blocking properties or those which inhibit the metabolism of the antipsychotics at the CYP450 enzyme level), lithium (especially when used with lithium), antiretroviral therapy (by inhibiting the metabolism of antipsychotics), concomitant use of medications like terazosin (which is alpha-1-selective adrenergic antagonist), tamsulosin, prazosin, alfuzosin, hydralazine, sildenafil, tadalafil, and vancomycin. While evaluating the patients besides the medications, other causes of priapism such as malignancies, trauma to the perineum, use of medications like testosterone, gonadotropin releasing hormone, heparin, warfarin, alprostadil, papaverine, propofol, methylphenidate, atomoxetine, scorpion sting, black widow spider sting should also be kept in mind.[11,90] Additionally, metabolic disorders such as amyloidosis, gout and substance use such as alcohol, cannabis and cocaine should also be enquired.[11,90]

While establishing the diagnosis, the clinician should make effort to distinguish the high flow and low-flow priapism. The antipsychotic induced priapism is usually low-flow ischemic type of priapism. The high-flow priapism is non-painful and characterised by retention of well-oxygenated blood in the corpora cavernosa, whereas the low-flow priapism is painful and is characterized by accumulation of deoxygenated blood, is prolonged, and can lead to irreversible damage.

Patients with priapism usually present with prolonged erection, which may or may not be painful. While history taking the clinicians should focus on collecting information about the duration of erection, level of pain, and past history of prolonged painful erections. Additionally, information with respect to all the ongoing medications, use of any erectorgenic medications in the recent past, use of opioids or other drugs of abuse, and haematological abnormalities such as sickle cell anaemia or other hemoglobinopathies and hypercoagulable states, and history of trauma to the local site must be enquired (Table-7). The local examination should focus on proper examination of genitalia, perineum, and abdomen. While examining the penis, the clinician should try to distinguish the ischemic low flow priapism from the high-flow priapism (in ischemic priapism, the glans will be soft, but the corpora is fully rigid and tender) (Table-7). The specific investigations in patients with priapism will include assessment of coagulation profile and carrying out corporal blood gas analysis that can aid in distinguishing arterial and ischemic priapism (Table-8).

Management involves removing the offending agent(s) and penile aspiration. If this does not help than use of phenylephrine or surgical intervention (penile shunt surgery) may be considered (Table-9).

Urinary Retention

Occasional patients on psychotropics can present with acute urinary retention. Some of the patients may also present with chronic urinary retention. The urinary retention is linked to the anticholinergic and adrenergic side effects of psychotropic medications. The available data in

the form of metanalysis suggest that the incidence of urinary retention with antidepressants (especially TCAs and SNRIs > SSRIs) is higher than the placebo.[91] Similarly, urinary retention has also been reported with antipsychotics, such as phenothiazines (chlorpromazine, thioridazine) and thioxanthenes (chloroprotixen), olanzapine clozapine, diazepam, baclofen, amphetamines, carbamazepine, and opioid analgesics.[12,91–93]

Available data suggest that elderly are at higher risk of medication related urinary retention and this is attributed to presence of benign prostatic hyperplasia. Additional risk factors include concomitant use of other medications, such as anticholinergic agents, opioids, alpha-adrenoreceptor agonists, benzodiazepines, NSAIDs, calcium channel blockers and detrusor relaxants that could also contribute to urinary retention.[94]

Assessment of a patient presenting with urinary retention require review of all the medications, looking for other anticholinergic side effects, and considering other causes of urinary retention (such as bladder stone, urethral stricture, meatal stenosis, paraphimosis, phimosis, penile constricting bands, prostate cancer, or any other external mass blocking the urinary passage). Additionally, infective (like, prostatitis, balanitis, and prostatic abscess), traumatic (penile trauma, abscess, and laceration) and neurological (for example, Guillain-Barre Syndrome, spinal cord lesions, herpes zoster, diabetic neuropathy, etc.) causes of urinary retention must also be ruled out.[12] In females, who present with acute urinary retention, causes like organ prolapse (cystocele, rectocele, uterine prolapse), pelvic mass (gynaecologic malignancy, uterine fibroid, ovarian cyst), retroverted impacted gravid uterus, acute vulvovaginitis, vaginal lichen planus, vaginal lichen sclerosis, vaginal pemphigus and dysfunction of the urethral sphincter should be kept in mind.[12]

The investigation panel (Table-8) is determined by the possible differential diagnosis. The drug induced urinary retention can be managed by reducing the dose or stopping the offending agent(s) (Table-9).[12]

Conclusion

The present guidelines provide details of management of the patients who encounter medical emergencies due to psychotropic medications. These guidelines cover some of the specific manifestations like seizures, glaucoma, agranulocytosis, diabetic ketoacidosis, myocarditis, aspiration pneumonia, etc. have also been covered in these guidelines. It must be acknowledged that each patient's health conditions, medications profile, and impact of medications might be different, and cognizance should be taken of the seriousness of the medical emergency, the potential causal relationship with the psychotropic medications and the final necessity of the medication.

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Management of Medical Emergencies associated with psychotropic medications

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Introduction

Psychotropic medications form an integral part of the management of various psychiatric disorders. However, psychotropic medications are associated with specific side effects, which can manifest as medical emergencies. Some of these side effects are rare, whereas some are relatively more common (Table-1). Some of the medical emergencies arise due to the toxic doses of these medications. Some of these side effects are obvious (for example, acute dystonia, akathisia), and the association with the ongoing psychotropic medicines is easy to establish. If not identified in time and intervened, some side effects can lead to significant morbidity and mortality. However, for some of these side effects, a high index of suspicion is required, and there is a need to rule out other possible causes before attributing the side effect to the ongoing psychotropic medication.

This guideline provides an overview for evaluating patients presenting with medical emergencies due to the ongoing psychotropic medications or intake of psychotropics in overdose. It provides an overview of how to assess and manage patients presenting with these medical emergencies. These guidelines are not a substitute for clinical knowledge, and every patient presenting with these features will require individualized assessment and management. These guidelines are limited to the life-threatening medical emergencies for which a definite etiological association between psychotropics and medical emergencies is established, or the crisis is related to the overdose of the medication. We are aware of other life-threatening side effects of psychotropics that can present as medical emergencies. An association between these presentations and psychotropics is reported, but a definite causal association is not established.

Table-1: Medical Emergencies due to use of or overdose of Psychotropic Medications

Medical Emergencies	Commonly implicated medications
1. Acute dystonias	Antipsychotics (Typical > atypical)
2. Akathisia	Antipsychotics (Typical > atypical)
3. Neuroleptic malignant syndrome	Antipsychotics (Typical > atypical)
4. Anticholinergic syndrome	Antipsychotics
5. Serotonin syndrome	Antidepressants
6. Antipsychotic toxicity	Antipsychotics
7. Antidepressant toxicity	Antidepressants
8. Lithium Toxicity	Lithium

9. Valproate toxicity	Valproate
10. Carbamazepine toxicity	Carbamazepine
11. Benzodiazepines toxicity	Benzodiazepines

Acute Dystonias

Acute dystonia is characterized by sudden involuntary contraction of muscles resulting in repetitive or twisting movements. These are usually seen during the initial days of starting antipsychotic medications. This can manifest as focal dystonia (affecting only one part of the body) or generalized dystonia (involving all body parts). The dystonia can be painful to the sufferers.

The antipsychotic-induced dystonia is defined as *"sustained abnormal postures or muscle spasms that develop within seven days of starting antipsychotics or while rapidly increasing the dose of the antipsychotic medication, or of reducing the medication used to treat (or prevent) acute extrapyramidal symptoms (i.e., removal of anticholinergic agents)"* [1]. The literature has reported a vast prevalence range, varying from 2% to 90%[2]. The differential risk of acute dystonia with various antipsychotics is influenced by their differential dopamine-acetylcholine antagonism, with higher levels of dopamine acetylcholine antagonism associated with greater chances of developing acute dystonia.

It usually involves the neck muscles (cervical dystonia- torticollis) and manifests as head twisting/turning to one side, backward, or forward. Besides the neck muscles, the dystonias associated with the use of antipsychotics can affect the eyelids (manifest as blepharospasm), jaw (oro-mandibular dystonia manifesting as slurring of speech, drooling of saliva along with difficulty in chewing and swallowing), tongue (lingual dystonia), and laryngeal muscles (laryngeal dystonia, manifesting as difficulty in speaking). Sometimes the hands or only the fingers may be involved. Rarely the generalized form of acute dystonia may manifest as opisthotonus. Among the various forms, laryngeal dystonia can lead to striders and be life-threatening. Multiple risk factors have been identified for precipitation of acute dystonia associated with the use of antipsychotics (Table-2)[2].

Table-2: Risk factors for the development of Acute Dystonias with antipsychotics[2]

- Use of high potency antipsychotics, such as haloperidol, fluphenazine, pimozide
- Children and young adults (especially 10-19 years)
- Male sex (especially young males)
- Race
- Previous history of dystonic reactions (one of the most powerful predictors)
- Family history of dystonia
- Cocaine use
- Mood disorders
- Hypocalcemia/Hypoparathyroidism
- Hyperthyroidism
- Dehydration

A specific type of dystonia that involves eye muscles, known as an oculogyric crisis, can occur when the patient is on a stable dose of antipsychotics. The various precipitating factors for oculogyric crisis include the use of alcohol, some emotional stress, fatigue, and suggestibility[2].

In almost all cases (95%), acute dystonia manifests within four days of starting an antipsychotics or after a significant increase in the dose of the antipsychotic[2].

Differential diagnosis: In terms of differential diagnosis of acute dystonia induced by antipsychotics, the other medications which can cause acute dystonia must be considered, which can include metoclopramide[2]. Other differential diagnoses include dissociation, catatonia, tardive dystonia (usually seen after months to years of antipsychotic use and do not improve rapidly after the use of anticholinergic medications), temporal lobe epilepsy, which can lead to bizarre postures, and hypocalcemia.

While establishing the diagnosis of antipsychotic associated acute dystonia, the possibility of dystonia related to other medications (Table-3) and substance of abuse must also be kept in mind, as often antipsychotics are prescribed along with other concomitant agents and patients with mental illness also have a high prevalence of substance abuse.

Table-3: Medications and substances other than antipsychotics which have also been reported to cause acute dystonia[2]

- **Antiemetics:** metoclopramide
- **Antidepressants:** Selective serotonin reuptake inhibitors
- **Antianxiety drugs:** buspirone, diazepam
- **Triptans:** sumatriptan
- **Other medications:**Chloroquine, Hydroxychloroquine, amodiaquine, phenylpropanolamine
- **Substances of abuse:** cocaine, ecstasy (3,4 methylenedioxy-methamphetamine)

Management: Acute dystonia is an acute emergency that requires immediate intervention. Occurrence of dystonia can disrupt the therapeutic alliance. The management of acute dystonia involves the intramuscular or intravenous administration of an anticholinergic medication or an antihistaminic agent (Table-4). Usually, the symptoms resolve within 15-20 minutes. Most patients respond to the first dose of the injectable medication, with only very few patients requiring repetition of the second or third dose of drugs. However, suppose a patient does not respond to 2 doses of medication. In that case, a change in the medication used for the management of dystonia should be considered. If this does not lead to the desired result, then a diagnosis other than acute dystonia associated with antipsychotics should be considered.

Once the acute dystonia is managed with various agents, it is recommended to continue anticholinergic agents for at least 24 to 48 hours to avoid recurrence of acute dystonia. However, in routine clinical practice, the anticholinergic agents are continued up to 4 to 7 days.

Table-4: Stepwise management of antipsychotic associated acute dystonia

Step-1	Intramuscular or Intravenous anticholinergic/anti-histaminergic compounds such as benztropine (1–2 mg), biperiden (5 mg), or diphenhydramine (25–50 mg)→ resolves in 15-20 minutes with IM injection and in 5 minutes with IV injection Other Options: Diazepam (2–5 mg), or Lorazepam (1–2 mg) → Equally efficacious; Treatment of choice for acute laryngospasm Oculogyric crisis: oral clonazepam in divided doses ranging from 0.5 to 4 mg/day
Step-2	If an episode of acute dystonia persists after an initial dose of parenteral medication, a second dose of the same drug can be given about 30 minutes later
Step-3	Switch to a different medication

Step-4	Fails to respond→ consider an alternative diagnosis, e.g., the persistence of trismus, might point beyond dystonia to a dislocated jaw

In routine clinical practice, some clinicians prefer to use prophylactic anticholinergic agents rather than allowing acute dystonia to emerge. However, everyday use of anticholinergic agents is not recommended. The use of the prophylactic anticholinergic agents should consider the risk factors for the development of acute dystonia, type and dose of antipsychotic use, and the concomitant medications[2].

Akathisia

The term akathisia is derived from Greek and means *'inability to sit'*. It is characterized by a subjective feeling of inner restlessness and objective restlessness, as observed by others. A sense of dysphoria usually accompanies it and the patient complains of a mounting tension when the he/she tries to remain still. In terms of objective evidence, the patient would appear to have difficulty sitting/standing/lying at one place for a long time.

Acute akathisia is usually seen during the initial few hours or days of starting antipsychotics. The risk for developing acute akathisia is high in patients receiving antipsychotics for the first time, rapid escalation of antipsychotic doses, and polypharmacy with antipsychotics.

Different types of akathisia described in the literature include:

- Acute akathisia.
- Chronic akathisia (akathisia lasting for at least three months).
- Withdrawal akathisia (seen within six weeks of reduction in the dose or stopping of antipsychotics).
- Tardive akathisia (seen after a long duration of use of antipsychotics).

These must be considered in the differential diagnosis before the diagnosis of acute akathisia is made.

Management: The first step in managing akathisia involves proper assessment to confirm the diagnosis of akathisia. Assessment of akathisia consists in taking a good history and carrying out a physical examination to distinguish different types of akathisia and ruling out the other differential diagnoses (Table-5). Akathisia is also associated with a high risk of suicidal behavior. Hence, patients with akathisia should also be appropriately evaluated for suicidality. A commonly used scale to assess subjective and objective aspects of akathisia includes Barnes Akathisia Rating Scale (BARS). It is recommended that BARS should be used before starting or increasing the dose of antipsychotics.

Table-5: Differential diagnosis of akathisia

- **Agitation secondary to psychotic symptoms**
- **Non-akathisia psychotic dysphoria**
- **Restless leg syndrome**
- **Anxiety**
- **Agitation related to affective disorder**
- **Drug-withdrawal state**
- **Organicity *(delirium, head injury, hypoglycemia)***
- **Neurological disorders *(Parkinson's Dis, Huntington's Dis)***
- **Tardive dyskinesia**
- **Insomnia**

The treatment of akathisia involves a reduction in the dose of an offending antipsychotic agent or changing to another antipsychotic with a lower propensity to cause akathisia (low potency first-generation antipsychotic or a second antipsychotic medication, like quetiapine). Other options include the use of anti-akathisia medications. The various options include beta-blockers, $5HT_{2A}$receptor antagonists, anticholinergic agents, dopamine agonists, GABAergic agents, benzodiazepines, and Vitamin B_6 (Table-6). Beta-blockers are usually considered the first line and gold standard agent for the management of akathisia. However, it is important to remember that beta-blockers cannot be used in all patients. Some of the contraindications **for the use of** beta-blockers include hypotension, bradycardia, diabetes mellitus, asthma**,** and cardiac conduction defects. In such **a** situation**,** mirtazapine, which is a $5HT_{2A}$ receptor antagonist, is considered to be an alternative first-line agent. The second alternative medication includes vitamin B_6[3,4].

Table-6: Management of Akathisia

Beta-blockers	
Propranolol	40-80 mg/day
$5HT_{2A}$receptor antagonists	
Mirtazapine	15 mg/day
Mianserin	15 mg/day
Cyproheptadine	8-16 mg/day
Trazadone	100 mg/day
Anticholinergics	
Biperiden	2-6 mg/day
Benztropine	1.5-8mg/day
Trihexyphenidyl	2-10 mg/day
Benzodiazepine	
Lorazepam	1-2 mg/day
Clonazepam	0.5-1mg/day
Diazepam	5-15mg/day
GABA Receptors Agonists	
Pregabalin	50-100mg/day
Gabapentin	300-600mg/day
Antihistaminergic agents	
Promethazine	25-50mg/day
Others	
Vitamin B6 (Pyridoxine)	200 mg/day
N-acetylcysteine (NAC)	1000-2000 mg/day

Neuroleptic Malignant Syndrome (NMS), Serotonin Syndrome and Anticholinergic syndrome

Neuroleptic Malignant Syndrome

Various psychotropics can lead to life-threatening side effects, which have a typical clinical picture. These patients can present with neurological manifestations in rigidity, change in reflex response, and altered sensorium. Reviewing the history of medication intake, proper physical examination, and carrying out appropriate investigations are helpful clues to the diagnosis. These side effects include Neuroleptic malignant syndrome, serotonin syndrome,

and anticholinergic syndrome. If these syndromes are not recognized in time and managed appropriately, these can be life-threatening.

NMS is a rare but life-threatening idiosyncratic side effect of antipsychotic medications. It has been reported with almost all antipsychotic drugs. Besides antipsychotics, NMS has also been reported with other medications like mood stabilizers and metoclopramide. The incidence rate of NMS has varied across different studies and is influenced by various methodological issues. The available data suggest an incidence rate of 0.02 to 3.23%[5,6]. The typical picture of NMS is characterized by fever, rigidity, altered sensorium, and autonomic disturbances[7]. Various risk factors have been identified for the development of NMS (Table-7). In terms of etiology, different etiological mechanisms have been suggested, with one of the most accepted hypotheses suggesting the clinical picture of NMS to be an outcome of dopaminergic antagonism at the D2 receptors in the central nervous system, which triggers a cascade that impairs the thermoregulatory response of the body, which degrades the dissipation of heat and increased production of heat in the body[8,9].

Table-7: Risk Factors for NMS[8-13]

Treatment-related factors: initial phases of treatment (usually the first week of starting of antipsychotics, 90% of cases seen within ten days of starting of medication), faster titration rates, use of high doses of antipsychotics, use of parenteral antipsychotics, high potency antipsychotics are more often associated with NMS when compared to low potency medications, antipsychotic polypharmacy, concomitant use of antipsychotics and lithium
Patient-related demographic variables: Young age, advanced age, male gender
Past and family history: personal and family history of NMS
Comorbidities: **the** presence of CNS dopamine receptor dysfunction, malnutrition, multimorbidity, iron deficiency, trauma, infection
Psychiatric diagnosis: mood disorder, psychotic disorder, catatonia, agitation (leading to exhaustion)
Medical condition: postpartum period
Ambient conditions: warm and humid climate with a risk of dehydration
Other issues: use of physical restraints
Nutrition: malnutrition
Other Psychotropics associated with NMS: Antidepressants (sertraline, paroxetine, amitriptyline), Lithium, Carbamazepine
Other non-psychotropic medications associated with NMS: Metoclopramide, antiparkinsonian medications, Tetrabenazine

Clinical features: The clinical features of NMS are usually seen during the initial few days after starting antipsychotic medications. Majority of the patients who develop NMS do so within ten days of starting antipsychotic, with almost all cases beginning within 30 days of beginning antipsychotics[9]. However, this should not be understood as NMS cannot occur after this time frame. The typical picture of NMS is characterized by fever, rigidity (lead pipe), altered sensorium, and autonomic disturbances (increased heart rate, increased respiratory rate, excessive sweating, sustained or labile hypertension, and hypersalivation). Some of the authors have tried to define the evolution of NMS in 5 stages, with stage-5 being the most severe form characterized by extreme lead pipe rigidity, heart rate in the range of 130-150 beats per minute, systolic blood pressure ranging from 140-210 mm of Hg, diastolic blood pressure ranging from 100-110 mm of Hg, body temperature in the range of 39-42^{0}C, accompanied by catatonia and coma[14].

Diagnostic criteria: Different diagnostic criteria have been proposed by different authors, including Addonizio criteria[15], Adityanjee criteria[16], Caroff and Mann's criteria[17], Levenson's criteria[7], Nirenberg criteria[18], and Pope's criteria[19]. Diagnostic and Statistical Manual (DSM), the fifth revision[20,] has also provided the diagnostic criteria for NMS. All these criteria define NMS using similar features, with some variation given to different components, including the rise in serum creatine phosphokinase levels. According to DSM-5 criteria[20,] a patient is required to fulfill all the three primary criteria (exposure to the dopamine-blocking agent, severe muscle rigidity, fever) and at least two other measures (Diaphoresis, Dysphagia, Tremor, Incontinence, Altered level of consciousness, Mutism, Tachycardia, Elevated or labile blood pressure, Leukocytosis and Elevated creatine phosphokinase). Recently, a consensus criterion, i.e., International Expert Consensus NMS diagnostic criteria[21], has been developed, which gives variable weightage to different symptoms. In the end**,** a total score is calculated, with a cut-off of 74 indicative of **a** diagnosis of NMS equivalent to DSM-IV TR criteria[22].

Serotonin Syndrome

Serotonin syndrome is a life-threatening side effect arising due to serotonin toxicity. The clinical level of serotonin influences features of serotonin syndrome toxicity and the extreme end of the toxicity, and the term serotonin syndrome is primarily used denoting the same. It is usually seen in patients receiving more than one serotonergic agent, those receiving selective serotonin reuptake inhibitors with other medications, which can inhibit the metabolism of serotonergic agents at the CYP3A4 enzyme level and resultantly lead to an increase in the serotonin levels or patients with medication overdose. Many medications have been implicated in the development of serotonin syndrome (Table-8)[23-27].

Severe serotonin syndrome is usually reported in those using more than one serotonergic medication in therapeutic doses or doses more than recommended, especially when Monoamine oxidase inhibitors (MAOIs) are combined with another agent. If unrecognized, serotonin syndrome can be fatal and lead to death. The underlying mechanism for the development of serotonin syndrome includes an increase in the synthesis or release of serotonin, reduction in uptake or metabolism of serotonin, and direct activation of serotonin receptors[24-27].

Table-8: Medications that can lead to the development of serotonin syndrome (Adapted from[23-27])

Antidepressants • Monoamine oxidase inhibitors (MAOIs) • Selective serotonin reuptake inhibitors (SSRIs) • Serotonin-norepinephrine reuptake inhibitors (SNRIs) • Serotonin 2A receptor blockers • St. John's wort • Tricyclic antidepressants **Anxiolytics** • Buspirone **Mood stabilizers** • Lithium • Carbamazepine • Valproic acid	**Antimigraine drugs** • Ergot alkaloids • Triptans **Analgesics** • Cyclobenzaprine • Fentanyl • Meperidine • Tramadol • Pethidine • Tependalol **Amphetamines and derivatives** • 3,4-methylenedioxymethamphetamine(Ecstasy) • Dextroamphetamine • Methamphetamine • Sibutramine

Antipsychotics • Aripiprazole • Clozapine • Olanzapine • Quetiapine • Risperidone **Antiemetics** • Metoclopramide • Ondansetron	• Fenfluramine • Methylphenidate • Phentermine **Others** • Cocaine • Dextromethorphan • Linezolid • L-tryptophan • 5-hydroxytryptophan

Clinical Features: The clinical features of serotonin syndrome can vary as per the severity of the syndrome. The clinical features usually appear early, i.e., 6-24 hours after the ingestion of the offending agents. However, in some instances, the clinical presentation may be delayed. The classical triad of serotonin syndrome includes altered mental status, autonomic overactivity, and neuromuscular hyperactivity (Table-9)[23-26].

Diagnostic Criteria: Two different diagnostic criteria have been proposed to diagnose serotonin syndrome, i.e., Hunter criteria and Sternbach's criteria. The Hunter criteria are decision-making criteria, which consider the use of serotonergic agents and the presence of clonus. Accordingly, serotonin toxicity should be considered to be present if the patient has either of the following: spontaneous clonus, inducible clonus, and agitation or diaphoresis, ocular clonus and agitation or diaphoresis, tremor and hyperreflexia only, hypertonia along with the temperature of $>38^0$ C and ocular clonus or inducible clonus[27]. Sternbach's criteria require 3 out of the ten given clinical features, i.e., mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever. Additionally, these criteria also mention ruling out other etiologies and the absence of starting a neuroleptic agent or an increase in the dose of neuroleptics before the onset of signs and symptoms of serotonin syndrome[28].

Table-9: Clinical features of serotonin syndrome (Adapted from[24-28])

Clinical Features	Mild	Moderate	Severe
Mental state	Anxiety	Agitation, pressured speech, hypervigilance	Confusion, delirium
Temperature	Maybe normothermic	Hyperthermia	Severe hyperthermia
Autonomic disturbances		Mydriasis Excessive sweating Flushing	Hemodynamic/autonomic instability, increased bowel sounds
Neuromuscular	Hyperreflexia, inducible clonus	Sustained clonus Opsoclonus Myoclonus Tremor	Respiratory failure Rigidity

Anticholinergic syndrome

The anticholinergic syndrome arises due to intentional or accidental intake of anticholinergic medications or other compounds. The clinical manifestations are an outcome of antagonisms of acetylcholine in the brain and the peripheral nervous system. Therapeutic use

of drugs with high anticholinergic properties can also lead to precipitation of the anticholinergic syndrome.

Many medications have been reported to be associated with the development of anticholinergic syndrome (Table-10). However, it is essential to note that this is not the complete list, and many other medications have also been reported to have a variable level of anticholinergic properties. Various scales like the anticholinergic burden scale have been designed to assess the anticholinergic burden of different medications. The various risk factors for the development of anticholinergic syndrome include older age and medications with anticholinergic properties, which can have an additive effect. Other risk factors include the use of certain street drugs and herbal products/medications that also have high anticholinergic properties (Table-10)[29,30].

Table-10: Medications implicated for causing anticholinergic syndrome (Adapted from[29])

Class of medications	Medications/Other agents
Antidepressants	Tricyclic antidepressants (Amitriptyline, Imipramine, Desipramine, Doxepin, Clomipramine, Nortriptyline, Protriptyline), Mirtazapine
Anti-histamines	Diphenhydramine, Doxylamine, Promethazine, Chlorpheniramine, Cyproheptadine, Clemastin, Dexchlorpheniramine, Hydroxyzine, Doxylamine, Meclizine
Anti-tussives/ Bronchodilators	Dextromethorphan, Theophylline
Anti-psychotics	Chlorpromazine, Droperidol, Haloperidol, Quetiapine, Olanzapine, Clozapine, Thioridazine
Benzodiazepines	Alprazolam, Diazepam
Anticonvulsants	Carbamazepine, Valproic Acid
Anti-emetics	Hyoscine (scopolamine), Cyclizine, Meclizine
Gastrointestinal Medications	Cimetidine, Ranitidine
Antispasmodics	Clidinium, Dicyclomine, Hyoscyamine, Oxybutynin, Propantheline
Antibiotics	Ampicillin, Clindamycin, Gentamicin, Piperacillin, Vancomycin
Analgesics	Codeine, Oxycodone
Antiparkinsonian agents	Amantadine, Benztropine, Procyclidine, Biperiden, Trihexyphenidyl, Glycopyrrolate
Cardiac Medications	Atropine, Digoxin, Diltiazem, Captopril, Dipyridamole, Furosemide, Hydralazine, Isosorbide, Nifedipine
Steroids	Prednisolone, Corticosterone, Dexamethasone, Hydrocortisone,
Muscle relaxants	Oxybutynin, Hyoscyamine, Flavoxate, Hyoscyamine, Orphenadrine, Tolterodine, Belladonna
Topical ophthalmoplegic	Cyclopentolate, Homatropine, Tropicamide
Plants	Deadly nightshade (*Atropa belladonna*), jimsonweed, mandrake root, Lupin beans, Angel's Trumpet / Datura (see Figure 1)
Other	Oxybutynin, benztropine, glycopyrrolate
Herbal Products	Datura, Lupin seeds
Street drugs	Angel trumpet, Phencyclidine

Clinical Features: The clinical features of the anticholinergic syndrome can be quite variable, ranging from only mild cognitive syndromes to a full blow anticholinergic syndrome characterized by central and peripheral signs and symptoms (Table-11). The majority of the manifestations are due to the involvement of the muscarinic receptors. The anticholinergic syndrome may also worsen pre-existing medical conditions among the elderly, including precipitation of angina, congestive cardiac failure, severe constipation, urinary retention, and narrow-angle glaucoma. Hence, the elderly presenting with worsening conditions or these manifestations should also be evaluated for anticholinergic burden[29,30].

Diagnostic criteria: There are no specific diagnostic criteria for the anticholinergic syndrome. The diagnosis usually depended on the clinician's awareness about this condition and the ability to recognize the same symptoms[29,30].

Table-11: Clinical manifestations of anticholinergic syndrome[29]

Systems/Functioning	Symptoms
Central	Agitation and/or restlessness, Auditory and or visual hallucinations, Cognitive dysfunction including disturbances in attention and concentration, Confusion or delirium, Sedation Seizures
Thermoregulation	Hyperthermia
Gastrointestinal	Dry mouth, constipation, decreased bowel sounds, paralytic ileus
Cardiovascular	Tachycardia, Arrthymias and other conduction disturbances (widening of the QRS complex and prolongation of QT interval), hypotension and circulatory collapse, widened pulse pressure
Ophthalmological	Decreased lacrimal secretion, blurring of vision, dilated pupils, worsening of or development of narrow-angle glaucoma.
Urinary	Urinary retention
Skin	Dry skin, flushing, hot

Assessment:

Assessment of a patient presenting to the emergency with altered sensorium and autonomic and neurological symptoms should alter the psychiatrist about possible clinical presentation due to the ongoing psychotropic medications. However, the clinician should consider all possible organic causes for the altered sensorium before attributing the whole clinical presentation to the continuing medicines. It is also essential to understand that these syndromes associated with various groups of medications can also lead to multiple complications.

A good history, carrying out a proper physical examination, and the findings backed by appropriate investigations can help reach a diagnosis. For NMS, the clinician should focus on the temporal correlation of onset of symptoms with starting antipsychotic medication while taking history. Additionally, the dose of the antipsychotic used and the rate of increasing the antipsychotics should be thoroughly evaluated. Other issues to be considered include looking at the concomitant medications and comorbidities. During the physical examination, the clinician should focus on fever, rigidity, sensorium, dehydration, autonomic disturbances, the color of the urine, etc. Additionally, efforts should be made to rule out other differential diagnoses (Table-12) [9,23-27, 29,31].

For serotonin syndrome, while taking history, the clinician should focus on the prescribed serotonergic agents and inquire about the use of over-the-counter medications, illicit drugs, and various dietary supplements such as St John's wort ginseng, tryptophan, and appetite suppressants. While carrying out the physical examination, a close watch should be kept on the various vital parameters and autonomic abnormalities. The neurological examination should focus on the elicitation of clonus, as this is considered the cardinal manifestation of serotonin syndrome as per Hunter's criteria. An important fact to remember while carrying out the neurological examination is that hyperreflexia and clonus are more often seen in the lower limbs. The diagnosis is usually based on the high index of suspicion and ruling out another differential diagnosis (Table-12) [9,23-27, 29,31]. Besides the differential diagnosis listed in Table-8, a differential diagnosis of carcinoid syndrome must also be considered in a patient with serotonin syndrome[23-27].

Similarly, while history taking, if the anticholinergic syndrome is suspected, the clinician should focus on the whole prescription and evaluate the total anticholinergic burden, rather than just focusing on the single implicating agent. While carrying out a physical examination, attention must be paid to the skin, the blurring of vision, dryness of mouth, cardiovascular manifestations, urinary retention, and ataxia[29,30].

However, it sometimes becomes difficult to distinguish between NMS, serotonin syndrome, anticholinergic syndrome, and malignant hyperthermia. This is especially the case if the patient is on polypharmacy or when the medication history is not available or clear. In such a situation, it is important to focus on the specific manifestation of these syndromes (Table-13)[9,23-27, 29,31].

Table-12: Differential diagnosis for NMS, serotonin syndrome, and anticholinergic syndrome [9,23-27, 29,31]

- **Worsening of the primary illness or emergence of new psychiatric illness:** agitation due to the illness, the emergence of catatonia, malignant catatonia, agitated delirium
- **Infection:** Any kind of infection, including encephalitis or meningitis, sepsis, brain abscess, post-infection encephalomyelitis syndrome, tetanus, botulism
- **Environmental:** Heatstroke, head injury/trauma
- **Endocrine/metabolic:** Thyrotoxicosis, phaeochromocytoma, hypocalcemia, hypomagnesemia, hypoglycemia
- **Neurological:** Severe extrapyramidal side effects, non-convulsive status epilepticus, structural lesions involving the midbrain, stroke, meningitis, encephalitis
- **Toxic:** Malignant hyperthermia, serotonin syndrome, anticholinergic syndrome, salicylate poisoning, heavy metal (lead, arsenic, mercury) poisoning, lithium toxicity, carbamazepine toxicity, strychnine poisoning, valproate toxicity, antipsychotic toxicity, antidepressant toxicity, benzodiazepine toxicity, carbamate toxicity, phosphorous poisoning
- **Substance abuse (toxicity/withdrawal):** Hallucinogens, amphetamines, cocaine, alcohol/sedative (benzodiazepine) withdrawal
- **Dopamine agonist withdrawal:** Parkinson hyperpyrexia syndrome (as an outcome of discontinuation of antiparkinsonian medications)
- **Use of Dopamine depleting agents:** reserpine, tetrabenazine
- **Others:** Acute intermittent porphyria, systemic lupus erythematous
- **Autoimmune:** autoimmune encephalitis

Table-13: Distinguishing features of NMS, Serotonin Syndrome and anticholinergic syndrome[9,23-27, 29,31,32,33]

Variables	Neuroleptic Malignant Syndrome	Serotonin Syndrome	Anticholinergic syndrome	Malignant hyperthermia
Medication history	Dopamine antagonists	Serotonergic agents	Anticholinergic agents	Depolarizing muscle relaxants, such as succinylcholine and Inhalation anesthesia
Sensorium	Stupor, coma	Agitation, coma	Agitation, delirium	Agitation
Temperature	>41.1^{0}C	>41.1^{0}C	≤38.8^{0}C	≈46^{0}C
Blood Pressure	↑	↑	↑	↑
Heart rate	↑	↑	↑	↑
Respiratory rate	↑	↑	↑	↑
Pupils	Normal	Mydriasis	Mydriasis	Normal
Mucosa	Sialorrhea	Sialorrhea	Dryness	Normal
Skin	Pallor, increased sweating	Increased sweating	Dry, Red, Hot	Mottled, sweaty
Bowel sound	↑	↑	↓	↓
Reflexes	Brady-reflexia	Hyperreflexia, Clonus	Normal	Hyperreflexia
Muscle tone	Lead pipe rigidity in all muscles	Increased, primarily in the lower limbs	Normal	Rigor-mortis like rigidity
Creatinine Phosphokinase levels	↑			↑
White blood cell count	Leucocytosis			Leucocytosis
Myoglobinuria	Present			Present

Management:

The detailed workup of a patient suspected to have either of these syndromes requires stopping the offending medications, efforts to confirm the diagnosis, rule out another differential diagnosis, treating the syndrome, and preventing the development of complications (Figure-1).

The first step in managing these syndromes should include the stoppage of the offending agent(s). This is often straightforward in NMS and serotonin syndrome. However, it is often tricky in anticholinergic syndrome, especially among the elderly, who have multiple physical comorbidities and receive numerous medications with variable anticholinergic properties. Accordingly, while history taking especial emphasis must be given to look for the agent who was added in the last or whose doses were changed in the recent times. If such an agent is evident, the medication needs to be stopped, provided the symptoms are of mild severity. However, if such information is not available, all the medicines must be evaluated for their anticholinergic properties, and those with high anticholinergic burdens should be stopped. However, it is essential to remember that stopping these agents can destabilize the underlying

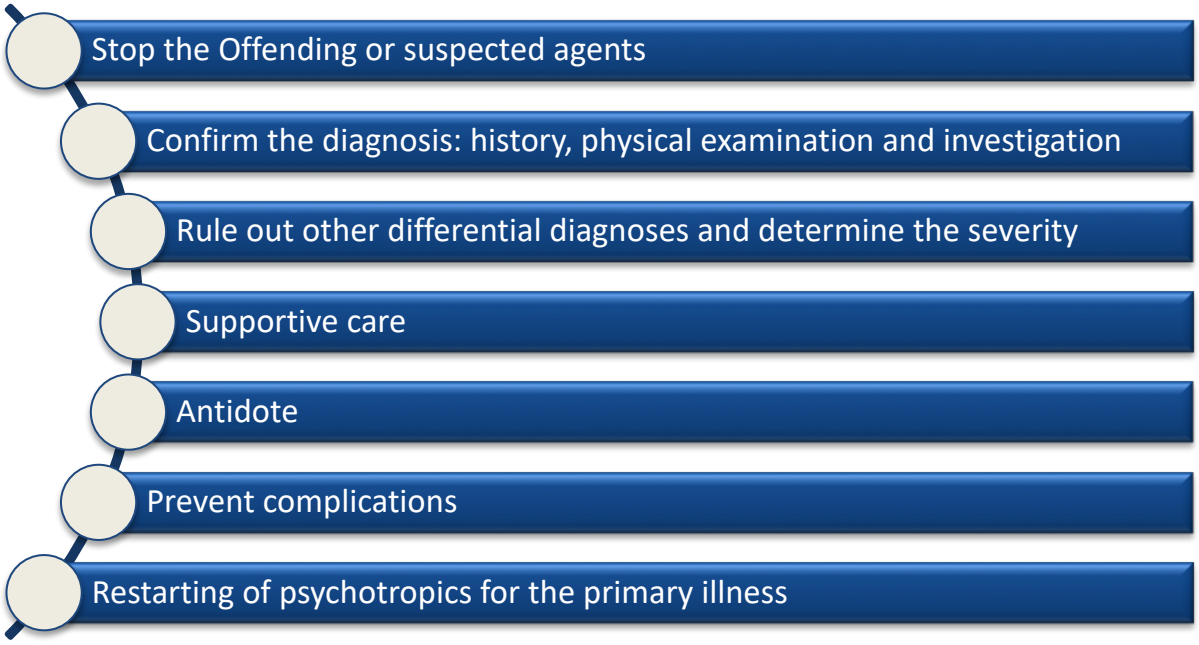
physical illnesses. Hence, appropriate substitute medications with low or no anticholinergic properties must be considered.

Investigations for patients suspected of this syndrome are also guided by the diagnosis and differential diagnoses being considered and the overall clinical picture (Table-14). In cases of the anticholinergic syndrome, detailed investigations are required in patients with severe anticholinergic syndrome only[9,23-27, 29,31].

Table-14: Investigations in a patient suspected to have NMS, Serotonin syndrome, or anticholinergic syndrome[9,23-27, 29,31]

- **Haemogram:** Leucocytosis is seen in patients with Neuroleptic Malignant Syndrome (NMS)
- **Creatine phosphokinase levels:** Elevation is significant; usually four times the normal is indicative of NMS (it is a reflection of muscle breakdown)
- **Urine for Myoglobin:** myoglobinuria suggests muscle breakdown in patients with NMS
- **Renal functions tests**
- **Serum electrolytes:** Sodium, potassium, calcium, phosphorous
- **Blood glucose levels**
- **Arterial Blood Gas (ABG) analysis**
- **Electrocardiogram (ECG)**
- **Liver function tests:** raised aspartate aminotransferase (AST), alanine aminotransferase (ALT), increased alkaline phosphatase.
- **Iron profile:** an iron deficiency may be associated with a poor prognosis
- **Blood Culture:** to rule out sepsis
- **Electroencephalogram (EEG):** Diffuse slowing may be seen
- **Coagulation profile**
- **Chest X-ray:** risk of aspiration needs to be considered
- **Cerebrospinal fluid analysis:** to rule out meningitis
- **Neuroimaging:** not required for diagnosis, but may be done if encephalitis and brain abscess is considered as the differential diagnosis
- **Serum and urine toxicological screening:** for salicylates, cocaine, amphetamines
- **Compression Ultrasound for Deep vein thrombosis**
- **Autoimmune panel:** if autoimmune encephalitis is being suspected

Figure-1: Steps in the management of NMS, Serotonin syndrome & Anticholinergic syndromes



Supportive care: Supportive measures are required to manage the symptoms and prevent the development of complications. These may include measures to reduce the temperature, treat or prevent dehydration, ensure proper nutrition, and avoid organ damage, such as renal impairment in patients with NMS. Supportive measures can also include the use of benzodiazepines, if the physical health permits, to manage agitation (Table-15). After initial stabilization, if required, gastrointestinal decontamination with activated charcoal may be considered in patients with anticholinergic syndrome if the history suggests recent intake (i.e., < 1 hour) of agents in overdoses[9,23-27, 29,31].

Table-15: Supportive measures in a patient suspected to have NMS, Serotonin syndrome, or anticholinergic syndrome[9,23-27, 29,31]

- Stop the offending antipsychotic medication or any other agent
- Decide about shifting the patient to an intensive care unit or a quiet place
- Manage airway, breathing, and circulation
- Monitor vitals
- Monitor blood pressure: patients with serotonin syndrome may require the use of antihypertensives; in patients with the anticholinergic syndrome, management of hypotension may require the use of bolus of crystalloids
- Manage hyperthermia by using cooling blankets along with the use of antipyretic agents to reduce the temperature
- Monitor the input and output, urinary catheter in case of urinary retention
- Intravenous fluids to address dehydration and prevention of kidney injury in patients with NMS
- Nutritional care: prevent and treat hypoglycemia
- Benzodiazepines, especially lorazepam to control agitation
- Early mobilization and physiotherapy to prevent deep vein thrombosis
- Heparin or other anticoagulants can be started for patients for whom early mobilization

is not possible
- Monitor for and treat seizures
- Prevent aspiration: proper positioning
- Sodium bicarbonate to alkalinize the urine to prevent renal failure in patients with NMS
- Addressing low iron levels in patients with NMS

Use of specific agents or antidotes: The particular agents for managing NMS include bromocriptine, dantrolene, amantadine, or dopamine agonists (Table-16). Among these agents, bromocriptine is one of the most commonly used agents, which can be given in doses of 10-40mg/day in divided doses. If the patient does not respond to these agents, ECT can be considered. It is important to remember that if ECT is considered, succinylcholine should be used cautiously, given NMS's common pathophysiology and malignant hyperthermia[9,31]. Mild cases of serotonin syndrome can be managed with supportive care and the addition of benzodiazepines. Moderate and severe cases will require the addition of serotonin antagonists, i.e., cyproheptadine. A loading dose of 12 mg orally or through a nasogastric tube, followed by 2 mg every two hourly until clinical improvement is seen or 8 mg, six hours after the symptoms have settled, is recommended. Severe cases of serotonin syndrome will require intensive supportive care to manage the symptoms and prevent complications (such as severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation, and acute respiratory distress syndrome) and administration of serotonin antagonists. Patients with severe serotonin syndrome may require muscle paralysis with non-depolarizing muscle relaxant, i.e., vecuronium. Opioids should be avoided in the management of serotonin syndrome. In patients with the anticholinergic syndrome, the use of Physostigmine may be considered. However, it is important to note that the use of Physostigmine is not without risk as it may worsen underlying physical health conditions like asthma, bronchitis, diabetes mellitus, cardiac problems, glaucoma, and psychosis[23-27].

Table-16: Pharmacotherapy for NMS[9,31]

Medication	Bromocriptine	Dantrolene	Amantadine	Dopamine agonists (Levo/Carbidopa)
Mechanism of action	Centrally acting dopamine agonist	Inhibition of calcium release from sarcoplasmic reticulum thereby causing skeletal muscle relaxation	Release of dopamine from nerve endings	Dopamine agonist
Route of administration	Oral	Oral and IV	Oral	Oral
Dose	10-40 mg per day in divided doses Max dose: 60 mg/d	Oral: 50-200 mg/d IV: 2-3 mg/kg/d to maximum of 10 mg/kg/d	100-300 mg BD	25-250 mg thrice or four times a day
Side effects	Hypotension Psychosis	Hepatoxicity	Hepatoxicity, Uncontrolled psychosis,	Psychosis, Myocardial infarction, arrhythmia

			Seizures	Dyskinesia

Restarting of psychotropics for the underlying mental illness: Once the symptoms of NMS resolve, it is usually recommended to restart the antipsychotics only after at least after two weeks of resolution of symptoms. Because of the risk of recurrence, it is always advisable to monitor the patient while rechallenging the patient with antipsychotics closely[9,31]. There is a lack of consensus on when to restart the antidepressants in patients with serotonin syndrome once the patient recovers from serotonin syndrome. Ideally, a gap of 1-2 weeks must be considered, and if started, the patient and caregivers should be psycho-education about the prevention of serotonin syndrome. This should include avoiding illicit drugs, prescription medications, dietary supplements, and herbal preparation that increase serotonergic transmission. Further, while restarting antidepressants, the doses should be increased slowly with close monitoring for symptoms of psychosis[23-27].

Psychotropic Toxicities and Overdose

Lithium Toxicity

Lithium has a narrow therapeutic window, and the therapeutic range for serum lithium varies from 0.4 to 1.2 mEq/Litre. The clinical features of lithium toxicity are usually seen when the serum lithium levels are >1.5 meq/Litre. However, it is essential to remember that the toxic effects of lithium may also be seen in patients with therapeutic serum levels. The life-threatening side effects of lithium usually appear when the serum level is > 2meq/Litre. In terms of toxicity, three different types of lithium toxicities have been described in the literature, which includes acute (primarily manifests with gastrointestinal symptoms, and may progress to neuromuscular signs and symptoms which usually appear after 2-3 days), acute on chronic (presents with both gastrointestinal and neurological symptoms) and chronic (present primarily with neurological symptoms) toxicity. Acute toxicity is usually seen in patients with lithium overdose. Chronic lithium toxicity is seen in patients who are on long-term lithium treatment. The toxicity manifestations are generally an outcome of either an alteration in the absorption or elimination of lithium levels. For example, any change in renal functioning (due to renal damage, hypovolemia, use of medications that increase lithium's reabsorption) can impair the elimination of lithium and resultant accumulation of lithium levels in the body (Table-18). Acute, chronic toxicity is seen in patients on long-term lithium, who take overdoses of lithium, either deliberately or accidentally[34-37].

Usually, the severity of lithium toxicity in patients with chronic lithium intoxication (i.e., those on long-term lithium therapy) is determined by the serum levels, with serum levels of 1.5 to 2.5 mEq/L suggestive of mild toxicity; levels of 2.5 to 3.5 mEq/L suggestive of moderate toxicity; and serum levels > 3.5 mEq/L suggestive of severe toxicity. According to serum levels, the clinical features may vary (Table-18), with patients with severe toxicity manifesting with stupor, seizures, and coma[34-37].

Table-18: Risk factors for lithium toxicity in patients on long-term lithium treatment

- Old age
- Hypovolemic shock
- Use of diuretics which increases the excretion of sodium
- Use of Angiotensin-Converting Enzyme (ACE) inhibitors: reduce the glomerular filtration rate and increases the reabsorption of lithium in the tubules
- Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which reduce the glomerular filtration rate and disrupt the renal prostaglandin synthesis
- Impaired renal functions

Table-18: Clinical features of chronic lithium intoxication[34-37]

System	Mild Toxicity Serum levels 1.5-2.5 mEq/L	Moderate Toxicity Serum levels 2.5-3.5 mEq/L	Severe Toxicity Serum levels >3.5 mEq/L
Neurological features	Fine tremors Fatigue Muscle weakness Hyperreflexia Gait abnormality	Coarse tremors Dysarthria Slurring of speech Ataxia Tinnitus Hypertonia Myoclonus	Stupor Seizures Coma Fasciculation Spasticity Rigidity Choreoathetosis Paresis Paralysis
Gastrointestinal features	Nausea Vomiting Diarrhoea	Nausea Vomiting Diarrhoea	Nausea Vomiting
Cardiovascular	T-wave changes Bradycardia Sinoatrial block Atrioventricular block	T-wave changes Bradycardia Sinoatrial block Atrioventricular block QRS prolongation	T-wave changes Bradycardia Sinoatrial block Atrioventricular block, Hypotension, Ventricular dysrhythmias
Renal			Renal failure

Valproate and Carbamazepine Toxicity

Valproate toxicity is usually seen following an intentional, homicidal, or accidental overdose. It mainly manifests with neurological signs and symptoms. The clinical features may involve the central nervous, cardio-respiratory, and gastrointestinal systems (Table-19).[38,39]

Table-19: Clinical Features of Valproate poisoning[38,39]

CNS manifestations

- Irritability, headache, ataxia
- Confusion, delirium, coma
- Dizziness
- Hallucinations
- Fever or hypothermia
- Agitation
- Constricted pupils
- Myoclonus

Cardio-respiratory Manifestations

- Hypotension
- Tachycardia & cardiac arrest (massive overdoses)
- Respiratory depression and apnea (massive overdoses)

Gastrointestinal manifestation

- Vomiting
- Diarrhea
- Hepatotoxicity
- Pancreatitis

Others

- Lethargy

Carbamazepine toxicity can result when carbamazepine is combined with other antiepileptic medications, other medications, and food products that act as enzyme inhibitors. In rare patients, carbamazepine may be a result of carbamazepine intentional overdose[40]. The appearance of clinical features may influence the formulation (i.e., immediate or sustained released formulations) and are dose-dependent. It is suggested that the symptoms may be slightly delayed to the erratic absorption of carbamazepine from the gastrointestinal tract.

The clinical features of toxicity can involve the gastrointestinal tract, central nervous system, and cardiovascular system (Table-20) (Table-20)[40,41].

Table-20: Clinical features of Carbamazepine toxicity[40,41]

Central Nervous System

- Sedation
- Dizziness
- Seizures, myoclonus
- Coma
- Nystagmus
- Confusion
- Dyskinesia
- Hyper/hyporeflexia
- Dysarthria
- Respiratory depression or respiratory arrest
- Mydriasis
- Double vision
- Cerebellar syndrome: ataxia, incoordination
- Anticholinergic effects

Gastrointestinal system

- Vomiting
- Anticholinergic effects- paralytic ileus

Cardiovascular system

- Hypotension
- Sinus tachycardia
- Arrhythmias

Others

- Anemia
- Rhabdomyolysis

Antipsychotic Overdose

Some of the patients with mental disorders may present in an emergency setting with antipsychotic overdose. The clinical manifestations of the antipsychotic toxicity are guided by the antipsychotic used in overdose and the dose of the antipsychotic medication. Other factors which can influence clinical manifestations include the age and the type of physical comorbidities present in the patient. The clinical features of the overdose are usually determined by the receptor profile of the various antipsychotics, as the toxic effects are generally the exaggerated effects of the pharmacological effects. Some of the essential receptors on which different antipsychotics act include the dopaminergic receptors (D2 antagonism), muscarinic receptors (M1 antagonism), histaminergic receptors (H1 antagonism), serotonergic receptors (5HT2A receptors), and alpha-adrenergic receptors. Various antipsychotic agents differ in these receptor profiles (Table-21)[42-44].

Table-21: Clinical Features of Antipsychotic toxicity or overdose[42-44]

General Clinical Features

Central Nervous System: sedation, CNS depression, coma, extrapyramidal side effects, NMS, delirium

Cardiovascular system: hypotension, tachycardia, arrhythmias, QTc prolongation, cardiac arrest

Antimuscarinic effects (anticholinergic toxicity- chlorpromazine, clozapine, olanzapine, and quetiapine): clinical features similar to the anticholinergic syndrome

Features that should be given attention for a specific antipsychotic overdose

- **Chlorpromazine:** drowsiness, sedation, coma, seizures, delirium, agitation, restlessness, arrhythmias, seizures, difficulty in breathing, urinary retention, dry mouth, blurring of vision, hypotension, skin rash, other anticholinergic side effects
- **Haloperidol:** EPS, akathisia, features of the anticholinergic syndrome, high or low blood pressure, QTc Prolongation
- **Clozapine:** Sedation, CNS depression, tachycardia, Agranulocytosis, sialorrhea, seizures, myocarditis, delirium, features of anticholinergic syndrome
- **Risperidone:** acute dystonia, hypotension
- **Ziprasidone, Amisulpride:** Sedation, CNS depression, QTc Prolongation
- **Amisulpride:** bradycardia, CNS depression, respiratory depression
- **Aripiprazole:** sedation, CNS depression, tachycardia, gastrointestinal upset, EPS
- **Olanzapine:** sedation, hypotension, QTc prolongation
- **Quetiapine:** orthostatic hypotension, tachycardia, delirium, anticholinergic syndrome

CNS Central Nervous System, EPS Extra-Pyramidal Symptoms

Antidepressant overdose

Occasionally some of the patients present to the emergency with antidepressant overdose. Usually, this is intentional but can also be intentional or iatrogenic in patients receiving polypharmacy with various antidepressants. As with antipsychotics, the clinical features of antidepressant overdose are also influenced by the type of antidepressant received, the dose is taken, intake of concomitant medications as part of the overdose, physical comorbidity (hepatic and renal impairment can influence the clearance of the medications), and the receptor profile of the antidepressants. Antidepressants with high serotonergic affinity may present with a clinical picture resembling serotonin syndrome. Patients with an overdose of tricyclic can have features suggestive of the anticholinergic syndrome (Table-22)[45].

Table-22: Clinical Features of antidepressant overdose[45]

Tricyclic Antidepressants

Central Nervous system: drowsiness, sedation, coma, convulsions, rigidity, EPS, delirium, respiratory depression, ophthalmoplegia **Cardiovascular system:** tachycardia, Prolonged QTc, ST/T wave changes, heart block, hypotension, cardiogenic shock, ventricular fibrillation, asystole **Anticholinergic effects:** Dry mouth, blurring of vision, mydriasis, urinary retention, paralytic ileus, fever/hyperthermia, myoclonus **Selective serotonin reuptake inhibitors** Clinical features suggestive of serotonin syndrome **Venlafaxine** Serotonin syndrome, gastrointestinal features, seizures, QTc prolongation, tachycardia, hypotension, delirium, coma **Bupropion** Seizures, hypoxia, cardiac arrest

EPS Extra-Pyramidal Symptoms

Benzodiazepine toxicity & poisoning

Benzodiazepines are one of the most commonly prescribed psychotropic medications both by the psychiatrist and other specialists. In a country like India, benzodiazepines are also sometimes available over the counter. Due to easy availability, these are one of the common medications which are used for an intentional overdose of the medications. At times, patients can present with accidental benzodiazepine overdose.

Benzodiazepine overdose and toxicity are usually not fatal in healthy adults, but they can be deadly in the elderly with multiple physical comorbidities[46].

The clinical presentation of the benzodiazepine overdose is influenced by the type of benzodiazepine, the dose ingested, type of physical comorbidities, and duration of use of benzodiazepine before the ingestion of overdose. Patients with the intake of lower overdose may present with drowsiness, dizziness, or sedation. However, patients with information of larger doses may present with more severe signs and symptoms (Table-23). The elderly are usually more vulnerable to develop respiratory depression. The risk of respiratory depression is higher among those with chronic obstructive respiratory disease, intake of higher doses, use of highly sedative and short-acting benzodiazepines like midazolam, triazolam, etc. The duration of respiratory depression may be prolonged in persons with liver dysfunction. Patients who have been using benzodiazepines for an extended period may develop withdrawal after recovering from the acute poisoning[46,47].

Table-23: Clinical Features of Benzodiazepine overdose[46,47]

• Sedation • Dizziness • Drowsiness • Slurring of speech, dysarthria • Blurring of vision • Confusion, stupor, coma • Nystagmus • Lethargy • Ataxia • Areflexia, hypotonia	• Seizures • Respiratory depression • Hypotension • Hypothermia • Paradoxical reaction- agitation, anxiety, disinhibition, aggression • Hallucinations • Combativeness • Anterograde amnesia • Atrioventricular block (rare)

Assessment & Management of Psychotropic toxicities and Overdoses

Assessment of a patient presenting to the emergency autonomic and neurological symptoms and or without altered sensorium should alter the psychiatrist about possible toxicity and overdose with one of the medications. However, the clinician should consider all possible organic causes for the altered sensorium before attributing the whole clinical presentation to the ongoing medication (Table-12). It is also essential to understand that these syndromes may also be associated with the use of other medicines too. Additionally, patients on psychotropics can also present with other medical emergencies (Table-24), other than NMS, serotonin syndrome, anticholinergic syndrome, and toxicity. These also must be considered in patients receiving psychotropics either in therapeutic doses or in overdose.

Table-24: Life-threatening side effects of psychotropics or medical emergencies arising due to side effects of psychotropics

Central Nervous system: Seizures **Cardiovascular System:** Myocarditis, cardiomyopathy, QTc Prolongation **Respiratory system**: Aspiration pneumonia **Gastrointestinal tract:** upper gastrointestinal bleed, pancreatitis **Haematological:** Agranulocytosis, eosinophilia **Endocrinological:** Diabetic ketoacidosis **Genital:** Priapism **Urological:** Urinary retention **Dermatological:** Steven Johnson syndrome, toxic epidermal necrolysis angioneurotic edema **Hepatic:** Hepatic failure, hyperammonemia **Ophthalmological:** Glaucoma

A good history, carrying out a proper physical examination, and the findings backed by appropriate investigations can help reach a diagnosis.

In terms of history taking, the clinician should focus on the type of medications being taken, duration of medication intake, doses of medications received, any history suggestive of suicidal behavior, the recent pattern of substance use, current medication adherence, recent physical health decompensation and relapse of primary psychiatric illness (Table-25).

Table-25: History and Physical Examination in patients presenting with psychotropic toxicity and overdose [34-37,38,40, 42-47]

- Type of medications received by the patient
- Duration of intake, doses used
- Any history of recent intentional or unintentional overdose
- If the overdose is suspected, try to ascertain the time of intake of overdose
- Concomitant medications including psychotropics, anticonvulsants, aspirin, and acetaminophen
- Symptom control of primary illness: worsening of the underlying illness-emergence of catatonia
- Substance use: recent use pattern, intoxication
- Any recent-onset physical decompensation: dehydration
- Antecedents of the current presentation: any psychosocial stressors, interpersonal issues, suicidal behavior (death wishes, suicidal ideations, recent attempt, lifetime suicidal attempt)
- Enquire about presence of any empty strips in the vicinity

- Recent serum levels (maybe reviewed for patients on lithium, valproate, carbamazepine)
- Recent renal function levels
- Adherence to medications
- Physical comorbidities
- Recent suicidal behavior
- Seizures
- Involuntary movements
- Gait

Physical examination

- Evaluate vitals: pulse, blood pressure, respiratory rate, temperature
- Proper neurological examination: tone of the muscles, reflexes, involuntary movements, myoclonus, gait, extrapyramidal side effects
- Proper cardiovascular examination: heart rate
- Signs and symptoms of hypovolemia
- Signs and symptoms of hypo- or hyperthermia
- Look for signs and symptoms of NMS, anticholinergic syndrome, serotonin syndrome

Investigations in patients presenting with suspected toxicity and overdose can be understood as routine investigations and investigations specific to the type of drug that is supposed to be taken in the toxic dose (Table-26).

Table-26: Investigations for patients presenting with psychotropic toxicity and overdose [34-37,38,40, 42-47]

- Serum Levels: Lithium, valproate, carbamazepine
- Renal functions tests
- Liver function tests: focus on alanine transferase
- Haemogram: focus on thrombocyte count
- Serum electrolytes: Sodium (hypernatremia), potassium, calcium (hypocalcemia), phosphorous
- Blood glucose levels
- Arterial Blood Gas (ABG) analysis
- Electrocardiogram (ECG)
- Liver function tests
- Blood Culture: to rule out sepsis
- Electroencephalogram (EEG)
- Urine analysis
- Pregnancy test
- **Chest X-ray:** risk of aspiration needs to be considered
- **Cerebrospinal fluid analysis:** to rule out meningitis
- **Neuroimaging:** not required for diagnosis, but may be done if encephalitis, stroke, or head trauma are considered as the differential diagnosis
- **Lumbar puncture:** not required for diagnosis but may be done if meningitis is a differential diagnosis
- **Serum and urine toxicological screening**
- **Compression Ultrasound for Deep vein thrombosis**
- **Haemogram**
- **Creatine phosphokinase levels:** to rule out NMS

Management: The management of psychotropic overdose can be understood as general supportive measures (Table-27) and measures specific to the type of medication taken in the overdose.

The history-taking should involve understanding the doses and duration of lithium use, concomitant medications, physical comorbidities, the status of the underlying psychiatric illness, adherence to medication, and recent suicidal behavior. The physical examination should also focus on eliciting the various signs of lithium toxicity (Table-20). The investigations should include ordering serum lithium levels and the renal function test. Other investigations are determined by the differential diagnoses being considered (Table-20)[34-37.]

If the valproate overdose is suspected, the history of intentional overdose or accidental overdose must be enquired from the patient and the family member. The family must be asked to look for empty strips and bottles of the medication to confirm the overdose. The diagnosis of valproate overdose is usually based on the history of a suspected overdose, raised serum transaminase levels, increased ammonia levels, and high serum valproate levels.

Whenever a person comes with a suspected overdose of carbamazepine while taking history, it is essential to focus on the doses taken, intake of concomitant medications, and intake of any medicines which can act as enzymes inducers or enzyme inhibitors, any food items which can act as enzyme inhibitors.

The investigations panel should include an assessment of serum valproate/ carbamazepine levels (serial examinations to monitor the serum carbamazepine levels) along with other investigations to rule out various differential diagnoses and evaluates the level of organ damage and complications due to valproate overdose[40].

Table-27: Supportive Management of for patients presenting with psychotropic toxicity and overdose [34-37,38,40, 42-47]

- Ensure airway, breathing, and circulation
- Decide about shifting the patient to an intensive care unit if the dose intake is heavy and the patient requires respiratory support
- Stop the offending agent if toxicity is suspected
- Monitor vitals
- Monitor blood pressure
- Intravenous access
- Monitor the input and output
- Nutritional care: prevent and treat hypoglycemia
- Early mobilization and physiotherapy to prevent deep vein thrombosis
- Heparin or other anticoagulants can be started for patients for whom early mobilization is not possible
- Prevent aspiration: proper positioning

Specific Measures for Lithium Toxicity: Specific measures for managing a patient with lithium toxicity involve stopping lithium, stopping the concomitant medications that may increase serum lithium levels, supportive care, and efforts to reduce the serum lithium levels. Additionally, gastric lavage with sodium polystyrene and whole bowel irrigation must be done if there is a history of recent lithium intake (i.e., < 1 hour). Intravenous fluids must be given to the patient to restore the glomerular filtration and normalization of urine output.

Haemodialysis should be considered in patients with serum levels of >2.5mEq/L in patients with chronic toxicity and >4mEq/L in patients with acute lithium toxicity. However, it is essential to note that hemodialysis may be considered in patients with serum levels lower than 2.5 mEq/L if renal impairment occurs.

The clinician may consider extracorporeal treatment in patients with serum levels >4mEq/L or who have altered sensorium, seizures, or are experiencing life-threatening dysrhythmias irrespective of the serum lithium levels. The haemodialysis should be continued till the serum lithium levels fall below 1mEq/L[34-37, 48,49].

Specific Measures for Valproate and Carbamazepine Toxicity: Management of valproate and carbamazepine toxicity involves stopping valproate/carbamazepine if the patient continues to take the same supportive care, and measures to remove valproate/carbamazepine from the body. Benzodiazepines may be used to manage seizures and agitation. The electrolyte imbalance must be corrected promptly[38,40].

If a patient presents with a recent valproate overdose (<2 hours), then gastric lavage with activated charcoal with a standard dose of 1 g/kg body weight with a maximum dose of 50 grams can be done. However, this should be avoided in sedated patients, and it is difficult to protect the airways. In patients with severe valproate toxicity, irrespective of the baseline renal function, hemodialysis may be considered[50,51]. In patients with severe valproate poisoning (i.e., serum valproate levels > 1300 mg/L, coma or respiratory depression requiring mechanical ventilation, severe acidosis (pH<7.10) and acute hyperammonemia encephalopathy and shock), extracorporeal treatment should be considered[38].

In terms of a specific antidote, naloxone (0.8 to 2mg, starting with 0.04 mg IV and slowly titrating up) and carnitine have been reported to be beneficial. However, the evidence for the use of these is not very robust. Naloxone has been reported to reverse CNS depression in patients with severe valproate poisoning[38,52]. Carnitine deficiency is supposed to mediate valproate-associated hyperammonemia and hepatotoxicity. Accordingly, the use of carnitine is reported to reduce these side effects. The recommended doses for L-carnitine include 100 mg/kg IV over 30 minutes (maximum of 6 g), followed by 50 mg/kg IV (maximum amount of 3 g) given every eight hours[53-55].

Management of carbamazepine toxicity is usually guided by the dose taken, signs, and symptoms. If the patient has recently taken the medication overdose, only activated charcoal binds carbamazepine in the gastrointestinal tract and resultantly does not allow it to be absorbed, maybe used[40]. However, precautions must be taken during the procedure to prevent aspiration. Other modalities suggested for the management of carbamazepine include hemodialysis, charcoal hemoperfusion, intravenous lipid emulsion, and venovenous hemodiafiltration[40, 56].

Specific Measures for Antipsychotic overdose: The first step in the assessment involves the ascertainment of the type of antipsychotic taken, the dose of the medication, and the use of concomitant medications. Further, it is also essential to ascertain the time since the intake of the medicines in the overdose. Initial supportive measures involve ascertainment of airways, breathing, and circulation. It is also essential to rule out other causes of similar clinical presentation, including various infections and another medication overdose (Table-12). The differential diagnosis of antipsychotic overdose could be identical to those noted for NMS and anticholinergic syndrome. It is essential to establish an intravenous line should be secured. Suppose the patient presents within one hour of the overdose of antipsychotic

medication. In that case, a single dose of activated charcoal can be given orally, provided the patient is willing to drink the same. It should not be given forcibly. If more than one hour has elapsed, then activated charcoal should not be used (Levine & Ruha, 2012). An ECG should be done to monitor the cardiac rate and rhythm. Depending on the clinical presentation and predominant symptoms, symptomatic management should be done. For seizures, benzodiazepines (intravenous lorazepam or diazepam) should be considered as first-line treatment. Patients with prolonged QTc interval (>500msec) should be administered 2-4 g of intravenous magnesium sulphate[43].

Specific Measures for Antidepressant overdose: As with antipsychotic overdose, the first step in the assessment involves ascertaining the type of antidepressant consumed, the dose of the medication, and the use of concomitant medications. Further, it is also vital to determine the time since the intake of the medicines in the overdose. Initial supportive measures involve ascertainment of airways, breathing, and circulation. It is also essential to rule out other causes of similar clinical presentation, including various infections and another medication overdose (Table-12). The differential diagnosis of antidepressant overdose could be identical to those noted for serotonin syndrome (Table-12). It is essential to establish an intravenous line should be secured. Suppose the patient presents within 1-2 hours of the overdose. In that case, a single dose of activated charcoal can be given orally, provided the patient is willing to drink the same, and the airways can be protected. Efforts should be made to reduce the chances of metabolic acidosis. For seizures, benzodiazepines (intravenous lorazepam or diazepam) should be considered as first-line treatment. The use of sodium bicarbonate should be considered in hemodynamically unstable patients, those experiencing seizures, and patients with QRS prolongation. The use of intralipid emulsion should be considered in patients who have consumed lipophilic TCAs in overdose and are hemodynamically unstable[45].

Specific Measures for Benzodiazepine Overdose: In terms of assessment, due care must be taken to maintain airways, prevent and manage respiratory depression, and prevent aspiration pneumonia. Gastric decontamination is usually not recommended; however may be considered in patients who have ingested substantial doses of benzodiazepines with or without ingestion of other medications in the last one hour; in such a patient, gastric decontamination with a single amount of activated charcoal should be considered if the patient is conscious and the airways can be managed[46,47].

Benzodiazepine-specific antidote includes the use of flumazenil in patients presenting with benzodiazepine overdose. It is a competitive benzodiazepine receptor antagonist, which can be helpful in the reversal of respiratory depression. However, its use is not without risk. Hence, it should be used selectively in patients with only benzodiazepine overdose. It is important to note that the efficacy of flumazenil to reverse respiratory depression is not consistent, and all the patients do not respond to the same[57].

Further, it is essential to remember that the use of flumazenil in patients receiving/taking a benzodiazepine for a long duration can precipitate a benzodiazepine withdrawal state and seizures. The use of flumazenil is associated with common side effects like gastrointestinal disturbances, and serious side effects can include supraventricular arrhythmias and seizures. Hence, it is essential to get a baseline ECG before starting flumazenil. When used, flumazenil should be used in the dose of 0.1 to 0.2 mg/minute (lower doses in children) intravenous over 30 minutes, repeated after at least one minute only if the patient does not achieve sufficient alertness and adequate respiration, to a maximum dose of 1-2 mg. Continuous infusion may be used to prevent resedation. Contraindication for the use of flumazenil are long term benzodiazepine users (therapeutically or abuse), epilepsy, raised intracranial pressure, arrhythmia, andn prolonged QTc or abnormal ECG[46,47].

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Management of Medication Induced Psychiatric Disorders

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Abstract: Drugs used in various clinical conditions for therapeutic purpose, though well tolerated in general, are associated with varied adverse events including psychiatric side effects (PSEs). They include all types of behavioural alterations mimicking any of the established psychiatric disorder. Such iatrogenic adverse effects interfere with management of both primary illness as well as resultant psychiatric manifestations. The mechanism involved in appearance of psychiatric manifestations due to medications is ill understood and beyond the scope of current discussion but the general observation is that those drugs with lipophilic properties cross blood brain barrier are notorious in affecting CNS functions. Changes in neuronal structure and function, neuronal signalling, imbalance in neurotransmitter functioning, impairment of neuro-steroid synthesis, dysregulation of mitochondrial function and similar mechanisms are attributed to neurotoxicity. The drugs also can cause cerebral insult indirectly through vascular, metabolic or electrolyte changes. A thorough knowledge and examination of any behavioural change in individuals who are on medication for physical disorders help in prevention and timely management of psychiatric side effects.

Introduction: Consultation Liaison Psychiatry by definition is the interface between psychiatry and other medical specialities and incudes the facilitation of medical treatment of patients in general hospital settings[1]. It is not uncommon to find patients, who are on medication for physical disorders, presenting with psychiatricsymptoms.However, it is very difficult find out whether the presenting psychiatric manifestations have occurred due to underlying disease or as adverse effects of the medication given primarily for the physical illness. Hence the psychiatrist and physician should have a thorough knowledge of the psychiatric side effects of various psychotropic and non-psychotropic medications. The inadvertent psychiatric side effects of medication used for therapeutic purposes could cause problems to the patient care in various ways like affecting the drug compliance, affecting the patient-physician relation and causing various psychiatric problems which might be harmful to the patient and their caretakers.

Hence, a holistic approach to evaluate such patients is of paramount importance. Inaccurate diagnosis of the condition might have harmful long term as well as short term implications

for the patient. It is difficult to confirm whether the presenting neuropsychiatric manifestations have occurred de novo or secondary to the medication used for medical illness or as a comorbidity of the psychiatric symptoms common with a psychiatric disorder. Establishing that the drug used for therapeutic purposes is the causative agent for the symptoms is critical because usually the effects caused by a drug are reversible and might disappear on discontinuing the drug.

Almost all kinds of drugs cause psychiatric side effects. According to a review study by Smith et al[2], majority (~65%) of drugs included in the Physicians' Desk Reference list cause potential psychiatric side effects.Since a long time, drugs have been shown to have neuropsychiatric side effects. In the 1960s, Reserpine, a drug used for hypertension, has been shown to cause depression as a result of likely monoamine depletion[45].The literature concerning the side effects of non - psychotropic medication does help in gaining knowledge about these drugs and how to manage the adverse effects. This article outlines the assessment and management of various psychiatric side effects of the drugs used for therapeutic purposes.However, discussing the psychiatric complications of all the drugs used for various medical conditions is beyond the scope of this article.

Assessment and Evaluation: There are certain risk factors that predispose the patient to develop psychiatric side effects after using medication. These could be related to the pharmacological properties of the drug, the type of treatment, or certain patient characteristics. Alomar et al.[3], in their study described some of these factors whichinclude high dosage of drugs, parenteral administration, narrow therapeutic index, polypharmacy, patients at extremes of age, patients with a prior mental illness, patients who are critically ill etc.,

Factors predisposing	**Example**
Drug related	Pharmacokinetics
	Pharmacodynamics
	Dosage
	Therapeutic Index
Treatment related	Route of administration
	Polypharmacy
	Duration of treatment
Patient related	Age, Gender
	Comorbidities
	Genetic Predisposition

Table 1: Factors predisposing a patient to psychiatric side effects

Mechanism:

As with any side effect, pharmacological mechanisms can be divided according to their pharmacokinetic or pharmacodynamic nature.

Pharmacodynamic mechanisms

- Both non psychotropic and psychotropic drugs influence the neurotransmitter systems directly or indirectly leading to an imbalance causing the psychiatric side effects.

Pharmacokinetic mechanisms

- Pharmacokinetic mechanisms are relevant when psychiatric side effects are known to follow a dose–response curve.
- Disease states, hepatic enzyme polymorphisms, and drug interactions leading to metabolic inhibition cause low clearance of the drug leading to increasing concentrations of the drug which lead to psychiatric manifestations.

Diagnosing a drug related psychiatric side effect could be complicated by many factors like physical illness, co-prescribed medication, non-prescribed agents and pre-existing mental illness. Criteria determining the causality of drug in the development of psychiatric side effects include:

- Temporal relationship between the drug exposure and the psychiatric side effect
- Evidence of the specific psychiatric side effects occurring with the suspected drug
- Plausible pharmacological mechanism for the psychiatric side effect (e.g. dopamine agonists and psychosis)
- Presence of alternative explanations for symptoms (e.g. pre-existing mental illness, de novo psychiatric illness, other drugs)
- Response of symptoms to the withdrawal of the drug
- Effect of re-challenge with the same drug.

Adverse drug reactions are generally classified into two groups

1. **Type A reactions: Augmented**
   These are predictable reactions that result from the medicine's usual pharmacological activity (although they can be unrelated to the intended clinical effect) and are commonly dose related. Most ADRs are of this type

2. **Type B reactions: Bizarre**
   These are idiosyncratic and unpredictable reactions that could not have been predicted from the known pharmacological activity of the medicine and are not dose related. They include hypersensitivity reactions mediated by immunological factors and true allergic reactions.

TYPE A	TYPE B
Predictable	Unpredictable
Usually dose dependent	Rarely dose dependent
High morbidity	Low morbidity
Low mortality	High mortality
Responds to dose reduction	Responds to drug withdrawal

Table 2: Types of Adverse Drug Reactions

Naranjo et al.[4], developed the ADR Probability scale(also known as Naranjo scale, Naranjo algorithm, or Naranjo Nomogram), a 10-item scale with good reliability and validity for predicting the probability of adverse reactions to drugs. This is shown below:

Questions	**Yes**	**No**	**Unknown/NA**
Are there previous *conclusive* reports on this reaction?	+1	0	0
Did the ADR appear after the suspected drug was administered?	+2	-1	0
Did the ADR improve when the drug was discontinued?	+1	0	0
Did the ADR appear with re-challenge?	+2	-1	0
Are there alternative causes for the ADR?	-1	+2	0
Did the reaction appear when placebo was given?	-1	+1	0
Was the drug detected in the blood at toxic levels?	+1	0	0
Was the ADR more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
Was the ADR confirmed by any objective evidence?	+1	0	0

Table 3: The ADR Probability Scale

The scores are then assessed as ≥9 = definite; 5–8 = probable; 1–4 = possible; ≤0 = doubtful. This scale helps in the clinical diagnosis of psychiatric side effects.

The World Health Organization Collaborating Centre for International Drug Monitoring - the Uppsala Monitoring Centre (WHO-UMC) has also put forth an assessing system to determine the causal relation between a drug and a suspected adverse reaction.

CAUSALITY TERM	**ASSESSMENT CRITERIA***
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake
	Cannot be explained by disease or other drugs
	Response to withdrawal plausible
	Event definitive pharmacologically or phenomenologically
	Rechallenge satisfactory, if necessary
Probable/Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Unlikely to be attributed to disease or other drugs

	Response to withdrawal clinically reasonable
	Rechallenge not required
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake
	Could also be explained by disease or other drugs
	Information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable
	Disease or other drugs provide plausible explanations
Conditional/Unclassified	Event or laboratory test abnormality
	More data for proper assessment needed, or
	Additional data under examination
Unassessable/ Unclassifiable	Report suggesting an adverse reaction
	Cannot be judged because information is insufficient or contradictory
	Data cannot be supplemented or verified

*All points should be reasonably complied with

Table 4:WHO-UMC causality categories

Psychotropic Drug Interactions:

Concomitant therapy with antipsychotics may result in pharmacokinetic interactions producing adverse reactions. Antipsychotics have poor metabolic clearance due to their large volume of distribution, lipophilicity and extensive protein binding.

First generation antipsychotics (FGAs) such as phenothiazines undergo biotransformation primarily by CYP2D6 with minor contributions from CYPs 1A2 and 3A4. Second generation antipsychotics (SGAs) phenothiazines undergo biotransformation primarily by CYP450s.Clinically significant interactions have been reported in patients taking fluoroquinolones or fluvoxamine which are potent inhibitors of CYP1A2. Drugs such as omeprazole, carbapazepine or rifampin and aryl-hydrocarbons in cigarette smoke can significantly lower clozapine and olanzapine levels, while discontinuation of these substances may result in rebounding clozapine levels leading to toxicity.

Tricyclic antidepressants (TCAs) undergo biotransformation by 4 major CYP450 (1A2, 2C9/19, 2D6 and 3A4). Clinically significant interactions involving TCAs are often the result of concomitant administration with other medications that inhibit CYP450 resulting in decreased TCA clearance. The majority of second-generation antidepressants (i.e. SSRIs)

undergo extensive hepatic oxidative metabolism mediated by CYP450 isoenzymes, however unlike the TCAs, newer antidepressants have a relatively wide therapeutic index, limiting the severity of adverse effects when concomitantly administered with enzyme inhibitors or inducers.Other newer antidepressants such as mirtazapine and reboxetine (European) have not been reported to result in clinically significant DDIs.

Common interactions involving BZDs often result in an increase in pharmacologic effects of the BZD due to either enhanced pharmacodynamic effects or pharmacokinetic interactions producing elevated serum BZD concentrations. The CYP3A4 system is primarily responsible for the metabolism of the majority of BZDs, followed by CYP2C19.

Interactions involving mood stabilizers may either be pharmacodynamic or pharmacokinetic. The most clinically relevant DDIs involving antiepileptic drugs (AEDs) used as mood stabilizers involve either the induction or inhibition of drug metabolism mediated by the CYP450 system.Drug interactions involving lithium involve changes in distribution or elimination of lithium by concomitantly administered drugs. Because lithium is treated like sodium, drugs that inhibit renal reabsorption of sodium at the proximal tubule (i.e. osmotic diuretics) result in reduced lithium concentrations. Other drugs such as theophylline and verapamil have also been shown to increase lithium clearance.[5]

Drugs causing psychiatric side effects: As described earlier, majority of prescribed drugs acting on various systems of the body can cause psychiatric side effects. Prior to describing each drug class in detail, a summary of the drugs causing psychiatric side effects is given below.

CLASS OF DRUGS	**EXAMPLES**
Cardiovascular Medications	Beta Blockers, ACE Inhibitors, Alpha agonists, Digoxin, Statins
Dermatological Medications	Cyclosporine A, methotrexate, infliximab, etanercept, ustekinumab, vemurafenib, and ipilimumab.
Central Nervous System Medications	Anticonvulsants, Anti Parkinsonian Drugs
Antimicrobials	Antibiotics, Antitubercular drugs, Antivirals, Antifungal drugs
Anticancer agents	Ifosfamide, 5-fluorouracil, asparaginase, vincristine
Immunomodulators	Interferons, interleukins, isotretinoin
Hormones	GnRH agonists, Progestins

Steroids	Corticosteroids, Anabolic Androgenic Steroids
Anaesthetic agents	Ketamine, Propofol, Suxamethonium
Oral Hypoglycemic agents	Metformin, Glimepiride
Muscle Relaxants	Baclofen, dantrolene
Respiratory System Drugs	Antihistamines, Decongestants
Reflux Medications	Proton Pump Inhibitors, H2 – Receptor Antagonists
Analgesics	Aspirin, ibuprofen, indomethacin

Table 5: Overview of drugs causing psychiatric side effects

Various psychiatric symptoms can be caused by the above-mentioned drugs. The table below outlines the various psychiatric symptoms and the drugs implicated.

SYMPTOM	**DRUGS IMPLICATED**
Anxiety	Steroids, Antivirals, Clonidine, Nitrates, Penicillins
Depression	Steroids, β blockers, clonidine, Antiretrovirals, GnRH agonists, H2 blockers, interferons
Delirium	ACE inhibitors, Steroids, antibiotics, anticholinergics, β blockers, H2 blockers
Insomnia	steroids, clonidine, proton pump inhibitors, quinolones, salbutamol, skeletal muscle relaxants.
Psychosis/hallucination/delusion	steroids, clonidine, proton pump inhibitors, quinolones, salbutamol, H2 blockers.
Manic reaction	Dopamine agonists, Antidepressants, Steroids, Sympathomimetics, H2 blockers, Thyroxine, Chloroquin, Baclofen
Sexual side effects	Diuretics, Anticonvulsants, Antihistamines, Muscle relaxants

Seizures	Antimalarials, Fluoroquinolones, Systemic steroids, CNS stimulants, Cyclosporine, tricyclics
Suicidal ideation	Nitrates, Antiretrovirals, Antifungals, Cycloserine, fluoroquinoles, IFN
Substance addiction	Cough Syrups, Steroids, Ketamine, Loperamide, Dextromethorphan
Cognitive dysfunction	H2 blockers, Corticosteroids, NSAIDs, anticonvulsants, antidepressants, anticholinergics

Table6: Psychiatric side effects and drugs implicated

Cardiovascular Drugs: Drugs acting on the cardiovascular system cause neuropsychiatric effects either directly (β-blockers) by crossing the blood-brain barrier and affecting the brain or indirectly (diuretics) by causing metabolic or electrolyte disturbances leading to psychiatric symptoms[6].

One important confounding factor to be considered while assessing a patient on cardiovascular drugs is the heart disease itself, on most of the patients with a cardiovascular disease have psychiatric symptoms. For example, depression and anxiety are common in post-MI patients, post CABG patients, patients with coronary artery disease[7,8,9]. Also, some of the critically ill patients in cardiac intensive care units have symptoms like mood lability, disorientation, hallucinations that characterize delirium. Hence, it is important to take proper clinical history while assessing a patient.

CLASS OF CARDIOVASCULAR DRUG	**SIDE EFFECTS**
β-blockers	Sedation, sleep impairment, psychosis, depression, dysphoria and delirium.
ACE Inhibitors	Altered mood, anxiety, fatigue, parasomnias, sedation and delirium.
Alpha Adrenergic agonists	Lethargy, depression, agitation, anxiety, confusion, delirium and psychosis.
Digoxin	Delirium, fatigue, depression, and psychosis
Diuretics	Fatigue, lethargy, malaise, anorexia, mania, depression and rarely delirium
Calcium Channel Blockers	Fatigue, sedation, confusion and delirium
Statins	Depression, fatigue, anxiety and occasional sleep disturbances.
Nitrates	Hallucinations, acute confusional state,

	delirium and rarely suicidal ideation.
Vasodilators	Fatigue, depression, mild anxiety, psychosis, and delirium

Table 7: Cardiovascular drugs and their psychiatric side effects

Dermatologicalmedications: Various drugs used for treating dermatological conditions like psoriasis, acne or dermatoses, cause neuropsychiatric side effects that range from mild headaches to encephalopathies[10].

DRUG	**SIDE EFFECTS**
Cyclosporine	headaches, tremors, paresthesias, overt psychosis, mania and seizures
Methotrexate	Psychosis and mania
Ipilimumab	Headaches, dizziness, lethargy, weakness, and transient sensory and motor peripheral neuropathies, MERS
IFN – 2αb	Depression, suicidal ideation
Tetracyclines, Isotretinoin, Acetretin	Headache, fatigue

Table 8: Dermatological drugs and their psychiatric side effects

Antimicrobial agents: Antibiotic drugs are used very commonly across the world and almost all groups of antibiotics are associated with a varied range of adverse neuropsychiatric effects.These can directly affect the functioning of the neuronal cells, cross the blood brain barrier and enter the brain or act on the microbiome in the gut and cause dysbiosis[11].

Antibiotic class	**Neuropsychiatric Adverse effects**
β-Lactams	Epilepsy
Macrolides	Dizziness, vertigo, tinnitus, anxiety, disorientation, psychosis, mania (antibiomania), hallucinations, deliriumand major depression
Fluoroquinolones	Headache,dizziness, somnolence and insomnia, peripheral neuropathy, psychosis, delirium, seizures and suicidal ideation/ behavior
Aminoglycosides	Peripheralneuropathy, encephalopathy, delirium and inhibition of neuromuscular transmission.
Polymyxins	Headache, dizziness, paresthesia, ataxia, convulsions and Apnea

Glycylcycline	Headache,dizziness and insomnia
Sulfonamides	Headache, drowsiness, tremor, aseptic meningitis, delirium, and psychosis
Nitrofurantoin	Headache, peripheral neuropathy, dizziness and drowsiness
Lipoglycopeptides	Agitation, restlessness, aggressiveness, visual and auditory hallucinations, psychosis and delirium

Table 9: Antibiotics and psychiatric side effects[11]

Antifungals: Many of the various types of antifungal treatments maycause neuropsychiatric side effects like confusion,agitation, myoclonus, hallucinations and, delirium. Some of these drugs cause the side effects by directly crossing the blood-brain barrier and some (Itraconazole) cause the side effects indirectly by affecting the neurotransmitter levels.
Amphotericin has been associated with various adverse effects like headache, neuropathy, convulsions, tremor, paresis, mood disorders, suicidal ideationand altered sensorium.

Antiparasitics: Antiparasitic drugs cause few neuropsychiatric adverse effects and most of these are related to the dead parasite rather than the drug itself. Some of the adverse effects include headache, dizziness, fatigue, convulsions, visual hallucinations and rarely delirium. The drugs include albendazole praziquantel, ivermectin, pyrantel and nitazoxanide.

Antimalarial drugs: Mefloquine is the most common antimalarial drug that is associated with psychiatric side effects. These include confusion, memory difficulties,impaired attention, depression, anxiety,paranoia and hallucinations.Headache, tinnitus, lightheadednessand dizziness are alsoobserved. In some patients receiving mefloquine, a condition characterized by convulsions, tremor and confusion called the "Postmalaria Syndrome" is seen. Quinine and chloroquine cause few neuropsychiatric adverse events.

Artemisinin derivative artesunate is associated with adverseeffects like headache, dizziness andtinnitus, peripheral neuropathy or isolatedparesthesia. Other artemisinin derivative artemether has been found to cause ataxia, clonus or sensory disturbance.

Antivirals: Antivirals like acyclovir and ganciclovir can cause lethargy, anxiety, hallucinations, and frank delirium when given in high doses. Depression, anxiety, hallucinations, and aggressive irritability have been reported with Foscarnet. Anti-HIV agents like Didanosine are associated with several psychiatric adverse effects like lethargy, depression, anxiety, emotional lability, delirium, insomnia, and psychosis. Severe suicidal ideation has been described with NNRTI like Efavirenz[12].

Disturbance in the gut microbiota due to antibiotics causes psychiatric side effects like major depressive disorder, autism, irritable bowel syndrome, bipolar disorder, schizophrenia, cognitive decline and anxiety disorders, especially with long term usage of the drugs.

Anti TB drugs: With tuberculosis still being a major health problem, anti tuberculosis agents are quite commonly used. Most of the regimensincludepolypharmacy which increase the chances of adverse effects. Some of the anti tuberculosis agents are associated with neuropsychiatric side effects.

Isoniazid is a first line anti tuberculosis drug that interfereswith pyridoxine-dependent coenzymesand may lead to vitamin B6 deficiency. This can affect the nervous system. Boththe peripheral and central nervous systems are affected by isoniazid. These side effects include restlessness, insomnia,headaches, muscle twitching, psychiatric symptoms, seizures, peripheral neuropathy, opticneuropathyand, rarely, cognitive decline[13].

Rifampicin, another first line anti tuberculosis drug is a potent inducer of both thehepatic and intestinalcytochrome P450 enzymesystems as well as the P-glycoprotein transportsystem[14].This isthe principalmechanism for CNS adverse effects. These include seizures, headache and drowsiness, ataxia and dizziness.

Other anti tuberculosis agents are also associated with CNS side effects. These are described in thetable below.

Drug	**Adverse effect**
Common (>10%)	
Cycloserine	Psychosis
Isoniazid	Headaches, seizures with overdosage
Linezolid	Headaches
Meropenem	Headaches
Ethionamide	Peripheral neuropathy
Aminoglycosides (amikacin, kanamycin most often)	Hearing loss
Thioacetazone	Tinnitus, giddiness
Occasional (1–10%)	
Cycloserine	Anxiety, headaches, seizure exacerbations
Ethionamide	Giddiness, headaches
Linezolid	Dizziness, insomnia, serotonin syndrome (if taking serotonergic medications)
Quinolones	Dizziness, headaches, insomnia, somnolence
Isoniazid	Peripheral neuropathy
Ethambutol	Retrobulbar optic neuropathy
Aminoglycosides	Vestibular dysfunction

Rare (<1%)	
Cycloserine	Agitation, bipolar exacerbations, dizziness, insomnia, slurred speech, suicide, tremor
Ethambutol	Confusion, dizziness, headaches, peripheral neuropathy
Ethionamide	Mental disturbance
Isoniazid	Agitation, altered mental status, ataxia, dizziness, insomnia, psychosis
Meropenem (with clavulanate)	Agitation, confusion, delirium, seizures, somnolence
Quinolones	Agitation, confusion, delirium, myoclonus and muscle jerks, psychosis, seizures, Tourette-like syndrome
Rifampicin	Ataxia, dizziness, drowsiness, headaches

Table 10: Neuropsychiatric side effects with antituberculosis agents[15]

AnticancerDrugs: Anticancer agents commonly cause neuropsychiatric side effects.Ifosfamide is known to cause frightening, vivid visual hallucinations at toxic doses[16].Occassionally, persistent psychosis can develop, with depressive mood, anxiety, terrifying hallucinations, insomnia, fear,delusion, disorganized speech, and persecution. Hypoactivity and negative symptoms can alternatewith hypomaniacal behaviour.

Procarbazine, an alkylating agent has been known to cause manic psychosis[17]. Drugs with immunomodulatory actions are often associated with psychiatric manifestations of CNS toxicity. Interferon α-2b, b and c are associated with depression, suicidal ideations and psychosis.Patients with pre-existing psychiatric illness are particularly prone for developing these side effects. IL-2 induces neuropsychiatric symptoms, especially hallucinations. Recurrentpsychotic episodes have been described also with IL-1 and rituximab[18].

Anti-Parkinsonian Drugs: Neuropsychiatric adverse effects are common with drugs used for PD like levodopa, dopamine receptor agonists,selegiline, amantadine and anticholinergicagents. These drugs cause severe disability to the patient and need to be carefully monitored.

According to a study done by Cummings[19], 30% of patients using parkinsonian drugs develop visual hallucinations,10% exhibit delusions and 15% have periodsof confusion. In addition, 10% experience anxiety,10% have euphoria and 1% have mania. Anxiety and sleep disturbances have also been reported with the use of these antiparkinsonian drugs.

Increasing age and dementia are the most common risk factors for neuropsychiatric adverse effects in patients with PD taking anti parkinsonian drugs. The risk is also found to be high in

patients receiving higher dosages of levodopa, adjunctive therapies such as amantadine and anticholinergics, or dopaminergic agonists.

Friedman[20]observed that the psychoses caused due to levodopa may be associated with a clear sensorium or occur against a background of confusion. The signs of impending psychoses include worsening sleep disturbance, including vivid dreams and nightmares. This slowly progresses tovisual hallucinations and paranoid/ grandiose delusions.Mania, anxiety and hypersexual behavior can also be seen. All of these symptoms occur in other psychiatric disorders and in PD itself, and cannot always be attributed to drugs. The neurochemical basis of drug-induced psychosis in patients with PD include chronic levodopa treatment stimulates dopaminergic receptors in the mesolimbic region and dysfunction of serotonergic pathways.

Patients with the above-mentioned risk factors are likely to develop delirium due to dopamine excess and acetylcholine deficiency, both in absolute amounts and/or relative to each other resulting in confusion, restlessness and floccillation.

DRUG	**PSYCHIATRIC SIDE EFFECTS**
L-dopa	Depression, hypomania, Visual hallucinations, sleep disturbance, abnormal dreams, cognitive impairment, psychosis, agitation, delirium
Dopamine agonists	Sedation, psychomotor agitation, anxiety, akathisia, sleep disturbance, hallucinations, psychosis, cognitive impairment, delirium
Amantadine	Decreased concentration, sleep disturbances, visual hallucinations, mood changes (irritability, anxiety, depression), fatigue, euphoria, psychosis, delirium
Selegiline	Sleep disturbances, agitation, psychosis
COMT inhibitors (Entacapone)	Sleep disturbances, hallucinations, delirium
Benztropine	Sedation, anxiety, psychosis, delirium, visual hallucinations, potential for misuse
Biperiden	Sedation, anxiety, psychosis, delirium, visual hallucinations
Orphenadrine, procyclidine	Agitation, anxiety, psychosis, delirium, visual hallucinations
Benzhexol	Agitation, anxiety, insomnia, psychosis, delirium, visual hallucinations, potential for misuse

Table 11: Neuropsychiatric side effects with antiparkinsonian drugs[12]

Anti-Convulsant Drugs: Psychiatric and behavioral side effects are very commonin patients taking antiepileptic drugs (AEDs). These adverse effects often cause several problems, both

to the patient as well as the treating physician by leading to poor adherence to the medication, sub optimal dosage and discontinuation of the treatment regimen. Between 15% and 20% of adult patients with epilepsy on AEDsdevelop these psychiatric and behavioral side effects. These include depressive mood, psychosis, increased irritability, and aggressive behavior. A betterunderstanding of the side effect profiles of individual AEDs ishighly important as it could help provide practical recommendationsand guidelines forprescribing AEDs.

DRUG	**PSYCHIATRIC SIDE EFFECTS**
Phenobarbital	Depression, sedation, sleep disturbances, psychosis, cognitive impairment, paradoxical agitation, delirium
Phenytoin	Agitation, insomnia, delirium
Primidone	Sedation, mood lability, psychotic symptoms, delirium
Benzodiazepines	Agitation, sedation, hallucinations, psychosis, cognitive impairment, delirium, withdrawal syndrome
Hydantoins	Similar to phenobarbital
Ethosuximide	Mood changes, irritability, sleep disturbances, psychosis, delirium
Sodium valproate	Sedation, hallucinations, depressive symptoms, delirium
Carbamazepine	Depression, agitation, sedation, psychosis, cognitive impairment, delirium
Vigabatrin	Agitation, lethargy, irritability, agitation, major depression, psychosis (‘schizophrenia-like’, in 2–4 % of treated patients), cognitive impairment
Topiramate	Psychosis (6 % of treated patients), depression, emotional lability, cognitive difficulties
Tiagabine	Psychosis (0.8 % of treated patients), depressive symptoms, sedation
Levetiracetam	Irritability, sedation and psychosis
Brivaracetam	Not significant
Gabapentin	Sedation, agitation, fatigue
Lamotrigine	Sedation, depression, agitation, psychosis (0.3% of treated patients)

Table 12: Neuropsychiatric side effects with anticonvulsant drugs[12]

Hormones:

Progestins and Estrogensused commonly in gynaecological practice, are the major hormones associated with psychiatric side effects. Progestins are associated with varied side effects like

anxiety, irritability, depression. Estrogens are usually associated with positive effects on mood and studies have been done to investigate the anti depressant effects of estrogen[12]. But these studies have provided inconsistent results.

Gonadotropin-releasing hormone (GnRH)agonistssuch as leuprolide and nafarelinare known to cause depressive symptoms[21]. Patients taking levothyroxine could develop anxiety, tremulousness, hyperactivity secondary to the development of levothyroxine-induced hyperthyroidism.

HORMONE	**SIDE EFFECT**
Progestins	Anxiety, irritability, depression
Estrogens	Euphoria, Manic reaction
GnRH agonists	Depression
Levothyroxine	Anxiety, tremulousness, hyperactivity

Table 13: Neuropsychiatric side effects with hormones

Immunomodulators associated with various psychiatric side effects, particularly depression. In most of the cases, the psychiatric complications occur within the first 3 months of starting the therapy. Using an anti depressant like SSRI helps to stabilize the symptoms. Certain studies have postulated that hypometabolismin the prefrontal cortex maypredispose certain patients to these neuropsychiatric side effects[22,23,24].

DRUG	**SIDE EFFECT**
NSAIDS (Aspirin, mefenamic acid, indomethacin, piroxicam, ibuprofen, naproxen, etc.)	Sleep disorders, fatigue, lethargy, agitation, anxiety, mood changes, hallucinations, psychosis, delirium
Corticosteroids	Lethargy, sleep disturbances, anxiety, agitation, euphoria, depression, personality changes, psychological dependence, psychosis, delirium
Cyclosporine A	Anxiety, depression, psychosis, cognitive impairment, delirium
Tacrolimus	Anxiety, depression, psychosis, delirium
Sulfasalazine	Sleep disturbances, delirium
H_1 receptor antagonists: cyproheptadine, cyclizine, promethazine, cetirizine	Sedation, agitation, psychosis, delirium
H_2 receptor antagonists: Cimetidine, famotidine, ranitidine, Interferons (α and β)	Agitation, lethargy anxiety, hallucinations, delirium, Sleep disturbance, depression, suicidal ideation, cognitive impairment, delirium
Methotrexate	Personality changes, irritability, delirium

Table 14: Psychiatric side-effects of immunomodulators[12]

Steroids:
Corticosteroidsare some of the most commonly prescribed medications for a varietyof diseases, likeasthma, allergic rhinitis, rheumatoidarthritis, inflammatory bowel disease, anddermatologic disorders. They are commonly associated with psychiatric side effects. These include mood changes, delirium, lethargy, insomnia, euphoria, depression, psychosis, personality changes, anxiety, and agitation. Usually, euphoria and hypomania develop with short term use and depression with long term use[25].

Increasing use of Anabolic androgenic steroidsillegally by some athletes and other bodybuilders has led to development of psychiatric side effects like acute paranoia, delirium,mania or hypomania, homicidal rage, aggression,and extreme mood swings, aswell as a marked increase in libido,irritability,agitation, and anger[26].

These side effects are usually dose dependent and resolve on discontinuing the medication. Occasionally, they might persist beyond one month despite medication.

Anaesthetics: Ketamine,an NMDA receptor antagonist, used as an anaesthetic is known to cause perceptual distortions, hallucinations, dissociation, referential ideas and schizophrenia like psychosis[27]. Propofol, another anaesthetic drug used for induction, is associated with side effects like dizziness, agitation, chills, somnolence and delirium.

Decongestants: Decongestants such as phenylephrine, pseudoephedrine,and naphazolinecan cause an atropine-likepsychosis that presents with confusion, disorientation,agitation, hallucinations, and memory problems.These drugs are contraindicated in patients taking MAO Inhibitors as they cause very high levels of norepinephrine leading to hypertensive crisis. Ephedrineis found to be associated with restlessness,dysphoria, irritability, anxiety, and insomnia[28].

Reflux medications: Both proton pump Inhibitors and H2 receptor antagonists are reported tocause seriousneuropsychiatricside effects like mentalconfusion, agitation, depression, and hallucinations. These occur rarely in the general population, but are more common in the elderly, and people with hepato-renal dysfunction.

H_2 receptor antagonist Cimetidine has significant drug interactions due to its non-selective cytochrome P450 inhibition. Itis known to increasethe blood level and action of tricyclic antidepressants, resulting intachycardia and other adverse effects. It is also associated with sexual dysfunction. Discontinuing ranitidine or cimetidine can induce a withdrawal syndrome that includes anxiety, insomnia, and irritability[29,30].

Vitamins: Vitamins play an important role in mental health. Various mental health conditions could develop due to vitamin deficiencies. Low levels of folate have been linked to depression. Symptoms such as memory loss, anxiety**,** depression, irritability, and insomnia are also associated with Vitamin B1 deficiency**.** Vitamin B12 deficiency is associated with mood

swings, paranoia, irritability, confusion, dementia, hallucinations and mania**.**Vitamin D deficiencyhas been associated with active mood disorder and depression. Some studies have shown that Vitamin D deficiency is associated with psychosis[31].

Other drugs: Ondansetron, a 5-hydroxytryptamine subclass 3 (5-HT3) antagonistused as an antiemeticis strongly associated withanxiety[32].Metformin, an oral hypoglycemic agent is known to cause anxiety, depression and confusion. Aminophylline and salbutamol are associatedwith agitation, insomnia, euphoria,and delirium[12].

The list of drugs causing psychiatric side effects is long and the types of psychiatric conditions due to various drugs used for other therapeutic indications are many. Following is a summary of some important drugs and major psychiatric manifestations.

	Psychotic symptoms	**Depression**	**Mania**	**Anxiety**
Amantadine	x	x	x	x
Aminoglycosides	x			
Amphetamines	x	x	x	x
Anabolic steroids	x	x	x	x
Anesthetics			x	
Anticholinergics	x	x		x
Antihistamines		x	x	
Antitubercular agents	x	x		x
Antivirals	x	x		x
Baclofen	x	x	x	x
Barbiturates	x	x	x	x
Benzodiazepines	x		x	x
β-Blockers	x	x	x	x
Bromocriptine	x		x	x
Cephalosporins	x		x	
Chloroquine	x	x	x	x
Clonidine	x	x	x	x
Corticosteroids	x	x	x	x
Digoxin	x	x	x	
Disulfiram	x	x	x	x
Interferon-α	x	x	x	x
Isotretinoin	x	x		
Levodopa	x	x	x	x
Lidocaine	x	x	x	x
Mefloquine	x	x	x	x
Methyldopa	x	x		x
Methylphenidate	x		x	x
Metoclopramide		x	x	x

Metronidazole	x			
Opioids	x	x	x	x
Oral contraceptives		x		x
Procainamide	x	x	x	x
Pseudoephedrine	x			x
Quinidine	x			x
Quinolones	x	x		x
Thiazide diuretics		x		

Table 15: Psychiatric side effects potentially induced by pharmacological treatment[47]

ElectrolyteImbalance: Many drugs used in various medical conditions are notorious in the development of disturbance in electrolyte concentrations which can result in psychiatric symptoms. The common condition physicians come across include hyponatremia. Drugs causing hyponatremia like diuretics, ACE inhibitors, anticonvulsants, proton pump inhibitors cause psychiatric side effects that include seizures, psychosis, acute confusion, coma.

MetabolicSyndromeDrugs that predispose a person to develop metabolic syndrome increase cardiovascular morbidity and mortality. There is an increase in incidenceof the syndrome among psychiatric patients because of factors like change in lifestyle, use of psychotropic drugs, genetic predipositions etc., Metabolic syndrome is further associated with the development of depression[33] and cognitive side effects and has become one of the greatest challenges in psychiatric practice[34].

Serotonin Syndromethough primarily caused by SSRIs, there are other drugs which can precipitate overactivation of 5HT2 receptors resulting in syndrome consisting of nausea, vomiting, diarrhoea, anxiety, agitation, lethargy, hypertension, altered sensorium and coma. Rarely if not recognized early, it can be life threatening.

Management of drug associated psychiatric side effects:

Consultation – liaison psychiatrists commonly encounter drug induced psychiatric symptoms in various clinical settings, especially the emergency services or critical care units. A thorough knowledge of these side effects is of high importance. Psychiatrists should work in coalition with the treating physician for the appropriate management of these side effects.

The diagnosis of medication induced psychiatric disorders is often post-hoc, and, in view of their similar presentation with the primary psychiatric illness, can be challenging.Therefore, almost any psychiatric symptom or syndrome could be considered as a potential psychiatric side effect, until its relation to the previous administration of drugs is proved beyond any doubt.A positive exposure, a positive dechallenge and a positive rechallenge is the best way to indicate a high probability. Many conditions other than drug induced psychiatric side effects need to be considered.

Diagnoses other than medication side effects	1. Underlying physical illnesses with psychiatric symptoms (eg, multiple sclerosis, systemic neoplasias, electrolytic disturbances, lupus erythematosus) 2. Aggravation of an existing psychiatric illness 3. Inaugural psychiatric decompensation in individuals with no evident susceptibility
Differential diagnoses among PSEs	1. PSEs at usual doses 2. Withdrawal-related PSEs. Side effects can occur after the discontinuation of antiparkinsonian agents, benzodiazepines, antipsychotics, antidepressants, anabolic androgen steroids, etc **3.** Intoxication-related PSEs

Table 15: Differential diagnoses of psychiatric side effects of medications[35]

Risk factors for the development of these side effects need to be assessed. The primary illness and any associated psychiatric complications should also be considered.

Investigations

The following laboratory and metabolic assessments are useful for a comprehensive diagnostic evaluation of the patient[36].

1. Complete blood picture (CBP)
2. Blood glucose levels
3. Liver function tests
4. Renal function tests
5. Thyroid function tests
6. Urine drug screening
7. Tests related to Syphilis, HIV, COVID
8. Chest X ray
9. ECG
10. Autoimmune screening
11. Assessment of Vitamin B12 and Vitamin D
12. Drug levels including alcohol concentration
13. Head computed tomography

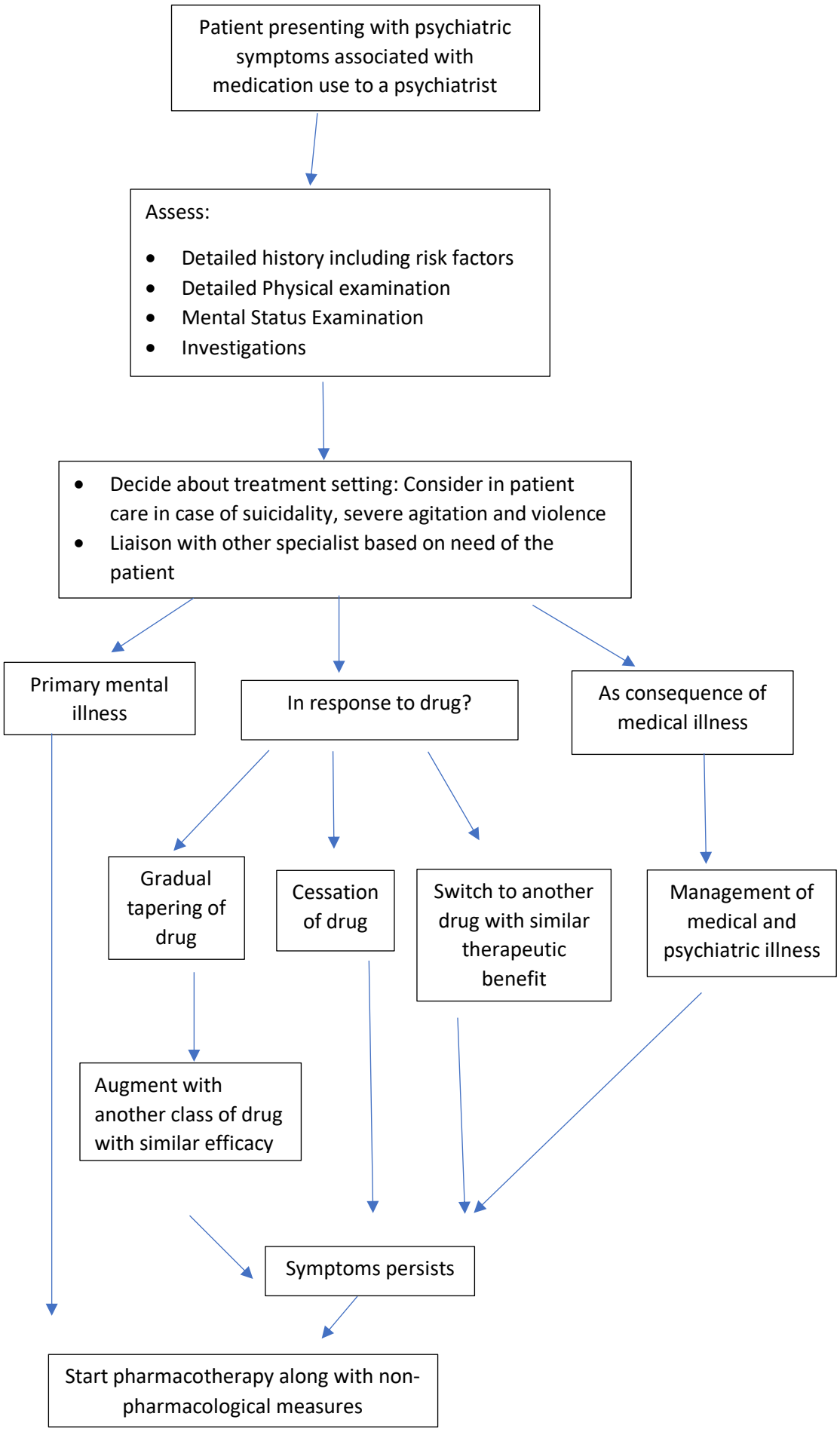
Pharmacological Management

The pharmacotherapy of the primary illness needs to be optimized to the patient based on his age, renal and hepatic status and comorbidities. In most of the cases, the symptoms are

reversible and remit with the cessation of the offending drug. Switching to another drug with similar therapeutic benefits is also helpful. However, appropriate psychotropics like antipsychotics, mood stabilizers might be necessary depending on the severity and duration of the symptoms. It is better to start the psychotropics at a minimal effective dose and taper the dose gradually according to the patient's condition. If the patient is unable to tolerate a particular psychotropic drug, a safer drug can be considered.

Non-Pharmacological Management

Non pharmacological measures like maintaining a familiar environment, re-orientation of the patient, regular visits by same personnel and family, psychoeducation of the patient as well as the family members also help in decreasing the psychiatric side effects. Close monitoring of the adverse effects of the psychotropic drugs is necessary. The following algorithm delineates


Patient presenting with psychiatric symptoms associated with medication use to a psychiatrist
Assess:
Detailed history including risk factors
Detailed Physical examination
Mental Status Examination
Investigations
Decide about treatment setting: Consider in patient care in case of suicidality, severe agitation and violence
Liaison with other specialist based on need of the patient
Primary mental illness
In response to drug?
As consequence of medical illness
Gradual tapering of drug
Cessation of drug
Switch to another drug with similar therapeutic benefit
Management of medical and psychiatric illness
Augment with another class of drug with similar efficacy
Symptoms persists
Start pharmacotherapy along with non-pharmacological measures

Conclusions:

- It is not uncommon to see patients presenting to a psychiatrist having co-morbid medical illnesses, for which they are using medication.
- There are no specific laboratory investigations or tests to differentiate primary mental illness from a psychiatric symptom secondary to medication use and presents a diagnostic challenge for the treating physician and psychiatrist.
- Psychiatric manifestations can be due to primary mental illness or induced by medications used for other therapeutic purposes or could also be secondary to some other adverse effect of the drug (e.g., psychosis secondary to hyponatremia, secondary to diuretic use).
- Almost all the drugs used for therapeutic purposes have psychiatric side effects.
- Identifying a medication as the definitive cause of psychiatric symptoms is difficult but helps in specific treatment. Evaluating patients presenting with psychiatric symptoms due to drugs prescribed for medical conditions is important because more often than not, the symptoms are reversible and there would be good recovery if the offending medication is discontinued.
- Constant liaison with the treating physician plays an important role in the management of the side effects.
- Management includes a holistic assessment and evaluation of the patient.
- The offending drug can be gradually tapered or stopped completely or switched to safer drug with similar therapeutic benefits.
- Non pharmacological measures like maintaining a homogenous environment, regular reorientation of the patient, regular visits by the family also help in the management of the psychiatric side effects in a critical care setting.

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Psychiatric Assessment in Consultation-Liaison settings

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Introduction

In the previous chapter we have understood the concept of consultation-liaison-psychiatry (CL-psychiatry) - its need, various models and settings in which they operate. Next, we move on to the assessment in CL-psychiatry settings. The basic structure of psychiatric assessment remains the same with detailed history taking, review of previous treatment documents and the mental status examination. But, apart from these there remains certain uniqueness in the assessment of patients in CL-psychiatry settings.

The uniqueness in Psychiatric assessment and communication in CL-settings [1,2]

The uniqueness remains within the name itself. While in individual clinical practice it is only 'consultation' -that is assessment followed by opinion or advice; in CL-psychiatry setting there remains both consultation and liaison with the primary treating team to form a collaborative opinion regarding the condition of the patient. Thus, in CL-psychiatry assessment, this liaison or communication holds the key which should be followed in its every steps. We can discuss them under following headings:

- **The mode of appointment of a psychiatrist with the patient in CL-settings**
  In individual consultation a patient comes directly to a consultant of personal choice, while in CL-setting a patient comes to the contact of only the designated consultants who are either integral part of the treating team or being referred to.
- **The need of appointment of a psychiatrist in CL-settings**
  In individual consultation, the need to contact a psychiatrist is a felt-need of the patient or the relative either by themselves or being guided by anybody. But in CL-setting, the need of appointment of a psychiatrist is felt by the primary treating team who feel there are certain issues where a psychiatrist would guide them better towards management of the patient.
- **The focus of assessment by a psychiatrist in CL-settings**
  In individual consultation, the focus of assessment of a psychiatrist is diagnosis and management of psychiatric disorders or problems which have caused impairment or difficulties in the personal-socio-occupational functioning of the patient.
  But in CL-settings, apart from the above, there can be many other areas of focus of assessment by a psychiatrist:
  - Whether the presenting psychiatric conditions in the medical setting are of primary psychiatric origin or secondary to the existing medical illness or its ongoing treatment
  - Whether ongoing psychotropic medications for patients with diagnosed psychiatric morbidity have impact on management of the ongoing medical illness
  - Whether the abnormal or uncooperative behaviors of the patients in wards are due to some psychiatric disorders or fall out of any bio-psycho-social issues
  - Whether there is any immediate risk of self-harm or harm to others by the patient
  - Whether there is any need to transfer the patient to psychiatric ward

- Whether there is any issues of privacy or medicolegal issues attached to particular cases (suicidal attempt vs accidental injury; any homicidal or sexual urge or advances; history of sexual abuse; any use of surreptitious medicines etc.)
- Assessment of mental conditions of patients whose sustained treatment compliance are matter of concern, like MDR Tb, ART in HIV
- Assessment of motivation and eligibility-preparedness of patients undergoing any major intervention -eg organ transplantation, cross-sex medical-surgical gender-affirmation interventions

- **The preparatory phase of assessment in CL-setting**

  In individual consultation, there is no preparatory phase between appointment and contact with the patient. But in CL-setting there should be a compulsory preparatory phase when the psychiatrist should do the following review:
  - Current Medical diagnosis and the ongoing treatment
  - Chart review of all available papers
  - Any past or ongoing history of psychiatric illness and their treatment
  - Direct communication with the treating/referring consultant to understand their conceptualization of the case and their need and focus of psychiatric assessment
  - For admitted patient, observation of the nursing staff or duty doctor in station
  - For admitted patient, sending information to the family member to be present at the time of interview

- **Introduction with the patient and family**

  During introduction with the patient in CL-psychiatry, disclosure of identity of the interviewer as psychiatrist at the outset may be little tricky. It might often be unexpected for the patient and relative to be interviewed by a psychiatrist and there may be emotional bias or stigma attached to it. Thus, depending on the situation, identity should be gradually revealed following establishment of rapport and maintaining optimum privacy.

- **Rapport building and its predicament**

  During any psychiatric interview, rapport building is the most sensitive and delicate part. In CL-setting, this job may be further difficult as the need for mental health service often remain unexpected here. The psychiatrist should explain the patients with common example that body and mind are inseparable. While anxiety affects our heart rate and respiration in one-hand; changes in body in high-fever affect our mental condition on the other. This makes the acceptance of psychiatrist easier for the patient and the family.

  Certain situations like paranoia, disorganized behaviors, substance use disorder, personality disorder or problems, dementia and delirium pose further problems. Delirium, being a very commonly encountered condition in CL-psychiatry, it needs special mention. In delirium, since fluctuating consciousness and attention is the main problem, here psychiatrist should talk gently, loudly, slowly -with one question at a time.

- **Psychiatric Interview and History taking** [3]

- Interview should begin with open narrative regarding current health problems and the distress associated with them
- Patient's experience with ongoing medical treatment particularly any difficulties in adjustment should be enquired
- Unlike individual consultation, in CL-psychiatry there may not be any spontaneous account on mental and behavioral issues of the patient
- Questions in this regard, may start with vegetative functions which are common issues for anybody
- Then the internalizing symptoms like presence of anxiety, somatic distress and low mood may be enquired
- Apart from the ongoing illness, any other recent or ongoing stressor and its impact on the patient not to be missed
- Any history of self-injury (suicidal or non-suicidal) should also be gathered along with any family history of such event
- Questions on externalizing symptoms of any agitation, anger, excitement, suspiciousness should follow
- Enquiry regarding hallucinatory behavior and disorganization -also important
- History of substance intake and their details must not be missed
- Patient's neuro-cognitive functions in daily-life situations particularly in case of elderly should be gathered. A common mnemonic 'Memory-LAPSE'–memory-language-attention-perceptuomotor-socialization-executive function may be helpful. For example, – any forgetfulness regarding recent events -where things kept –what is to be done –common names, address; any difficulties in finding right words; difficulties to focus and process information when interacting different persons together; any difficulties in usual activities of cooking-shaving; any recent oddities in socializing; difficulties in finance handling-decision making etc
- Family history of any mental illness should be enquired
- Patient's development history and personality features -particularly stress handling capacity, interpersonal relationship, emotional stability and impulsivity should be enquired
- Any religious and cultural influence on overall behavior or cognition of the patient should also be noted

- **Mental status examination (MSE)**

- In CL-psychiatry setting, since delirium is the most-common cause of referral, MSE may start with general inspection of behaviors suggestive of any disorganization (lying disheveled in bed, hallucinatory behaviors), agitation-floccillation (hands being tied to prevent picking-&-pulling of ports)
- It should be followed up with questions on orientation and patient's open narrative on ongoing distress
- During initial interaction catatonia should be ruled out from motor behavior and speech
- Organization of the speech and thought should be noted carefully
- Examination of affect is quintessential because depression, anxiety, adjustment difficulties are very common association in medical setting
- Complain of somatic distress or 'unexplained physical symptoms' being very common in medical setting, signs of depression-anxiety, obsession-hypochondriasis must be

looked for. Apart from them, la-belle-indifference in affect, health-care seeking behavior and anything suggestive of secondary gain should also be looked into.

- Other than internalizing symptoms, if any elevated, expansive, irritable affect is noted, that should be followed with relevant examination of psychomotor activity, thought and perception – suggestive of mania
- Delusion and hallucination tried to be elicited carefully if the patient is found to be having hallucinatory behavior or showing guarded, evasive, hostile attitude.
- There must be customary assessment of any suicidal intent in every patient
- For patients with paranoid psychopathology, anger, excitement, any thoughts of causing harm to others should be probed
- A brief assessment of neuro-cognitive functions particularly in elderly and those having presented with such history
- Apart from these issues, assessment must also include patient's insight regarding the ongoing medical illness and the problems for which psychiatric assessment has been sought

- **Use of screening tools for assessment**

In CL-setting there may be paucity of time for detailed psychiatric assessment. For this purpose, few standardized screening tools have been developed for quick screening of common psychopathology in primary-care or other specialized medical setting. These tools can be used by trained mental health professionals or even primary care personnel before confirmatory diagnosis by psychiatrists. So, this **training of the primary care personnel** about proper use of these screening tools is also an essential part of CL-psychiatry practice.

Basic characteristics of the tools should be:

- Short, easy and quick to apply
- Locally developed or adapted and translated versions in local language are more appropriate
- They should be appropriate for particular age group under examination
- Tools may be of two types –
    i. **Targeting broad psychopathology** like internalizing symptoms of depression, anxiety, panic, somatic symptoms, stress-trauma - all in one tool - **PRIME-MD-PHQ** (Primary care evaluation of mental disorders-patient health questionnaire or its brief version **BPHQ** (Brief- patient health questionnaire) [4]
    ii. **Targeting specific psychiatric disorder** like **PHQ-9**[5] (a 9-item questionnaire for depression), **GAD-7**[6] (Generalized anxiety disorder-7-item) for anxiety, **PHQ-15**[7] (A 15-item Patient Health Questionnaire) for evaluating severity of somatic symptoms. All these self-rated questionnaires are developed from PRIME-MD-PHQ.
- There are plenty of other screening tools customized for particular symptoms, age group and situation of assessment, which will be discussed subsequently.

Apart from general history taking, MSE and application of screening tools – assessment of certain situations warrants special mention in CL-psychiatry assessment. They are as follows -

- **Assessment of immediate risk to self and others:**

Agitation, excitement and violence in a patient always presses a panic button in a medical setting for which referral comes to psychiatrist for assessment of immediate risk to self and others. That can be clinically assessed by:

- **Observation**
  - Violent behavior
  - Possession of weapon
  - Self-destruction
  - Extreme agitation or restlessness
  - Bizarre/ disorientated behavior
- **Reporting of**
  - Reporting of death wish, suicidal urge
  - Thoughts of hopelessness, intolerability, inescapability and desperation along with marked anxiety, insomnia
  - Verbal commands to do harm to self or others, that the person is unable to resist (command hallucinations)
  - Trait impulsivity and Recent violent behavior

- **Assessment of uncooperative behaviors causing Management Problem**

  Another issue of major concern, is uncooperative behavior in the ward in apparent clear consciousness - like not following ward norms or treatment advice, pressing for early discharge, giving suicidal threats, complaining against treating staffs etc. Apart from ruling out underlying depression and psychosis, here the assessment should focus more on the psycho-social aspects of the patient –
  - Patients' understanding of the medical and ward advice communicated to them and their apprehension regarding those issue
  - Any miscommunication or mistrust with the treating team
  - Degree of discrepancy in the background milieu of the patient and that of the hospital
  - Personality – negative affectivity, impulsivity, ability to adjust to a new situation and new persons
  - Perceived role deficits of the patient when away from home, for example a patient living alone with pets in home may become anxious and press for discharge to look after them

- **Request for Transfer of patient to psychiatry ward**
  - This request usually comes for patients with apparent immediate risk to self or others as mentioned above.
  - First thing to rule out is delirium because in delirium patients may turn violent in a state of confusion. The behavioral presentation of delirium may become the major concern for the treating team, but the principal concern for the patient is the underlying medical cause.
  - Another is substance intoxication and withdrawal where the apparent behavior abnormality often may have serious medical underpinning and an expression of delirium

- Management of delirium should continue in medical ward with regular psychiatric observation
- Substance use disorder patients may be shifted to psychiatry ward after initial stabilization of medical complications
- Patients with depression, suicidality or psychosis with serious medical morbidity where chance of medical emergency may emerge at any time should also be managed in medical ward with regular psychiatric supervision
- In stable medical conditions – like not keeping any ports or requiring oxygen therapy, patient may be shifted to psychiatry ward with provision of regular observation by the medical team

- **Formulation of the diagnosis and related notes:**
- Provisional or differential diagnoses of psychiatric disorders or problems as per current nosology of DSM or ICD
- Probable etiology of the psychiatric condition in the background of medical illness – any mutual causative role, or comorbidity, or any coincidence
- Probable interaction of the required psychiatric treatment with ongoing medical treatment and the treatment milieu
- There should be also some comment on biopsychosocial background of the patient which may be relevant regarding overall management of the case, like developmental issues (low intelligence, intellectual disability, autism), any ongoing stressor in personal life, personality, etc.
- Any evidence of immediate risk to self and others and need or decision regarding transfer to psychiatry ward
- Any adjustment needed on the part of the treating team to manage uncooperative behavior of the patient

- **Mode of communication to the referring team**
  In CL psychiatry, apart from putting down notes on papers certain additional things are advisable:
- Psychiatrist should communicate directly to the treating consultant at least via telephonic conversation
- Mitigate all the doubts regarding the case from mental health perspective and overall formulation
- Formulate a comprehensive treatment plan

- **Communication to the patient and family**
  In liaison practice the referred consultant usually do not give any direct therapeutic advice to the patient or family, but there must be some transparent and supportive communication with them regarding:
- Explanation regarding how mental health issues is pertinent in this case
- Why the primary treating team has sought for psychiatric assessment and opinion
- Impression of CL-psychiatrist regarding presence of any psychiatric morbidity and current severity
- If any risk of immediate self-harm or harm to others or any ongoing strain to treatment milieu

- Role of family members to help the patient adjust to the treatment milieu, for example if there is any obligation of the patient back home – that should be taken care properly by relatives
- How provision of mental health support or treatment along with the primary treatment services would improve the overall outcome
- One very important issue in liaison-practice is to ensure that there is no discrepancy in communication between the primary treating team and the liaison specialist.

- **Plan for follow-up**
- In cases of confirmed major psychiatric diagnoses where pharmacological treatment needs to be started, follow up should be there at least within a week
- For those patients, regular follow-up at psychiatry OPD after discharge is also must
- Their treatment response can be evaluated by serial MSE or with different rating scales as in case of individual consultation
- In cases where definitive psychiatric diagnosis could not be reached, regular follow up is necessary with need for psychometric evaluation and symptomatic management

Now we proceed further to –

Assessment of psychiatric conditions in individual CL psychiatry settings as per their need

Here, discussion would not be done as a psychiatric or medical diagnosis but as a clinical-problem as perceived by the primary treating team in liaison services. We would divide this section under five groups:

I. Psychiatric assessment at Emergency Resuscitation (ER) units
II. Psychiatric assessment at intensive care units (ICU)
III. Assessment at non-emergency and chronic care units of different specialties
IV. Assessment of need for medical-work-up in patients undergoing treatment in psychiatry units
V. Multidisciplinary Assessment at medical boards

I. Psychiatric assessment at ER:

In emergency setting, referral is the usual model of CL-psychiatry practice. For quick assessment of **urgency of psychiatric attention**, the primary care personnel in the ER may be trained with a screening tool named **MHTS**[8] (Mental Health Triage Scale). In MHTS, the behavioral problems are arranged in five categories of urgency for psychiatric assessment

- Immediate (red) – Immediate need of mental health response along with referral to security or Police - due to violent aggression / possessing weapon / self-destruction attempt
- Emergency (orange) – Very urgent need of mental health response (usually within 4 hours) – clear-cut intent, plan and arrangement for committing harm to self or others; - very high-risk behavior associated with confusion and disorganized behavior

- Urgent (yellow) – need of mental health response within 24 hour – expression of suicidal intent (no clear-cut plan yet); rapidly increasing confusion, psychotic behavior (delusion, hallucination, disorganization)
- Semi-urgent (green) – need within 72 hours – major psychiatric disorders of mood or apparent psychosis without any suicidal intent; uncooperative behaviors in ward like wandering, refusing medicines and other ward norms
- Non-urgent (blue) – need within 4 weeks – known psychiatric disorders stable on medication which need regular follow up

A recent Indian study[9] on emergency psychiatry referral in a tertiary care hospital using MHTS found that the degree of urgency corroborated with the severity of scoring in **BPRS[10]** (Brief Psychiatric Rating Scale) and yellow was the most common zone of referral.

Now we discuss some of those conditions according to commonality of their presentation and urgency of assessment:

- **Confusion with behavioral abnormalities**

These are the most common cause for referral in Indian liaison settings [9,11]. Such referral raises the possibilities of either a neurocognitive disorder (delirium) where the consciousness, attention, orientation are the primary deficits with psycho-motor and thought-perceptual disturbances; or it may be another primary psychiatric condition with behavioral disorganization where there is inattention and difficulty in assessing consciousness and orientation.

Assessment for Delirium

- Delirium is an acute (onset within 2 weeks) neurocognitive syndrome which at times may be prolonged up to six months.
- There may be a plethora of presentation -
    - Variable psycho-motor disturbances (hyperactive, hypoactive or mixed)
    - Perceptual disturbances (hallucination, illusion)
    - Thought abnormalities (disorganization or delusions).
- Thus, the Hyperactive variety is often mistaken for psychosis and hypoactive for depression. The hyperactive variety is the more common presentation in ER.[11]
- But the primary deficit areas are attention, consciousness and comprehension leading to disturbed orientation, memory and other cognitive dysfunctions.
- Very important feature of delirium is fleeting and fluctuating presentation with time – particularly worsening after evening or 'Sun-downing phenomena'.
- Another characteristic behavior feature of delirium is floccillation - picking and pulling of objects around
- Since, primary impairment is inattention, during assessment one has to talk slowly, clearly and loudly and not many questions at a time.
- For early recognition of delirium and to prevent being misdiagnosed as psychosis or depression, health care personnel at medical setting may be trained with some screening tools.[12] Among them **NEECHAM[13]** (Neelon and Champagne) Confusion Scale is one of the most suitable screening instruments in medical and surgical wards.

- Delirium occurs only secondary to some medical condition or existing dementia (particularly Lewy body and Fronto-temporal dementia)
- Thus, after clinical confirmation of delirium, causes of delirium should be searched for by history, examination and investigation.
- Metabolic, autoimmune and infective are the 3 main etiology behind delirium which would require relevant investigations in blood and cerebrospinal-fluid (CSF). Neuroimaging should also be done to rule out any cerebral lesion.
- Delirium may also occur due to acute intoxication and withdrawal of addictive substances, psychotropic drugs and exposure or overdose to certain drugs
    - Anticholinergics (commonly referred as atropine psychosis)
    - Antimalarials (commonly referred as chloroquine psychosis)
    - Diuretics and other hyponatremic drugs,
    - Corticosteroids and other immunosuppressant drugs like azathioprine
    - Dopaminergic antiparkinsonian drugs like levodopa
    - Antitubercular (particularly isoniazid, cycloserine, ethambutol)
    - Antibiotics particularly fluroquinolones,
    - Antiretroviral (particularly efavirenz, zidovudine),
    - Antimetabolite (particularly 5-furouracil) etc.
- Another important condition is post-ictal state in epilepsy or non-convulsive status epilepticus or NCSE, which can only be established by prolonged EEG recording with the help expert epileptologists.

Assessment of other primary psychiatric conditions with confusion like presentations [14]

Presentation with acute disorganized behavior may appear as confusion. It may be a symptom of psychosis particularly acute psychotic conditions like ATPD (acute and transient psychotic disorders) with apparent confusion and polymorphic features of psychomotor and thought-perceptual disturbances. Puerperal psychosis very commonly presents like this. But with increasing knowledge we are gradually coming to know that many of these acute psychotic conditions are auto-immune origin -particularly NMDA-encephalitis. Thus, in acute onset (few weeks) disorganized behaviors predominantly in young females (age < 45 year) with confusion and particularly convulsion – autoimmune encephalitis must be ruled out.

At times psychotic conditions like schizophrenia and mania may also present in a grossly non-goal directed excitatory condition with marked hallucinatory behaviors – which may be considered as catatonic excitement historically described as delirious mania by Kraepelin. In these cases, influence of psychoactive substances must also be ruled out.

At times dissociative conditions with anxiety and agitation may also present with experiences of Deja phenomenon and depersonalization-derealization which may appear as confusion - historically described as hysterical psychosis. These often happen in trans-cultural background or may follow acute stressor or trauma.

These diagnoses should come only after exclusion of delirium.

- **Intoxication and withdrawal of addictive substances [14]**

Substance use related disorders come second to delirium regarding overall cause of referral to psychiatry.[11] In ER, the need for psychiatric service is due to:

- Patients often remain confused, aggressive with immediate threat to self and others
- Physicians may need psychiatrists' knowledge about medical complications of intoxication and withdrawal of different substances and their interactions
- After immediate stabilization of patients, psychiatrists' role would be important for subsequent detoxification
- Long term management plan would depend on assessment of degree of severity of the substance use disorder – like isolated or established harmful use or dependence. This can be done with the help of diagnostic guidelines of ICD/DSM or screening tool like **AUDIT**[15] (Alcohol Use Disorder Identification Test) for the most commonly used substance alcohol.

- **Self-Injurious (SI) attempts** [14,16]

Any SI attempts outside the hospital premises are always brought to the ER first and after initial medical stabilization of the patient, referral to a psychiatrist is obligatory.

In the preparatory phase of assessment, the psychiatrists should enquire about the following:

- Observation of any aggressive behavior in ward
- Any evidence of substance intoxication or withdrawal
- Any records of ongoing or previous mental illnesses and their treatment
- Any history of ongoing chronic debilitating or fatal medical illness and their treatment

With this available information, psychiatrist would further proceed towards interview of relative:

- Any history of past and family history of SI
- If any previous SI attempts - nature, lethality and expressed intent in that attempt
- Regarding current SI - in what circumstances and time - that occurred
- How the patient was recovered
- Any suicide note was recovered or not
- Any history of psycho-social stressor like bereavement, financial loss, or acute incident of shame-guilt or anger-altercation or temper-tantrum
- Any recent discussion regarding hopelessness, death, or warison
- Patient's family structure, social support
- Usual sleep pattern and any recent insomnia
- Any behaviors suggestive of impulsivity, emotional dysregulation, aggression in personality
- Personality pattern regarding stress handling, adjustment to a new situation and inter-personal relationship
- Any history of developmental delay or diversity

After talking to the informant, a customary MSE must include examination of

- Affect – any sadness, emptiness or despondency
- Cognition of worthlessness, inescapabilty, intolerability, desperation
- Any persecutory thoughts or hallucinatory experiences (particularly commanding voice)

- Detailed interview regarding SI attempt -
  - Intent of the SI – an attempt to die/ or a sudden expression of anger, frustration, protest/ or an attempt to relieve anxiety
  - In case of death wish – reason for that – to get relief from an inescapable, intolerable situation (temporary shame-guilt/ or ongoing worthlessness, hopelessness/ or helplessness out of fear of harm) /or an attempt to meet a beloved dead person
  - Whether the commission of the act – at the heat of the moment/ or with any prior plan /or any activities as a part of a group /or reaction to some commanding voices from air
  - If prior plan, or command – how long those were happening
  - If any previous attempt – what happened in those attempts – either self-restrained due to some reason or aborted by others – how the life was saved
- Apart from MSE, there can be application of standardized tools to determine chance of recurrence of suicide attempt based on the current severity of intent
  - **Beck's SSI** [17] (scale for suicidal ideation)-most commonly applied tool particularly in research -but the tool is not available for free use.
  - **C-SSRS** [18] (Columbia Suicide Severity Rating scale) - Another increasingly used tool which is free to use and has more extended dimensions. Apart from screening the current suicidal intent and rating of its intensity, it also screens for previous suicidal behavior or attempts which also include NSSI (Non-Suicidal Self Injury). There is also rating for degree of lethality of previous suicidal attempt.

With all these cross-sectional assessment – formulation should be done as follows:

- SI – suicidal or non-suicidal (NSSI)
- Any influence of substance – intoxication or withdrawal
- Any habitual NSSI – related to developmental diversity or personality (borderline) factors
- In suicidal SI – ascertain the possibility of grief, acute stress reaction, mood disorders and psychosis, associated anxiety, substance use disorder, personality disorder
- Risk of recurrence of suicidal SI – based on previous attempts, persisting thoughts of intolerance-inescapability-desperation and personality features of impulsivity, anxiety, aggression, scores in tools like SSI or C-SSRS
- Acceptance of need for hospitalization and adjustment to its milieu

Subsequent plan for further assessment at Psychiatry department:

- Establishing a definitive psychiatric diagnosis with fulfillment of nosological criteria
- Need for psychological assessment like personality by standardized tools TCI (Temperament-Character-Inventory) or IPDE (International Personality Disorder Examination), - if necessary -IQ assessment, for underlying psychodynamic processes projective tests like – Thematic Apperception Test (TAT), Rorschach Ink-Blot-Test (RIBT)
- Regular monitoring of suicidal intent by standardized tools – by SSI or C-SSRS

- **Sudden severe chest discomfort, respiratory distress and marked anxiety** [14,19]

This is also a very common presentation in ER where physicians do not find any respiratory or other systemic medical pathology and send referrals to CL-psychiatrists for psychiatric assessment and ruling out psychiatric etiology behind such presentations.

At the initiation of assessment, psychiatrists should keep in mind that they should not jump into searching for any primary psychiatric condition and take it for granted that all the underlying medical emergencies have been ruled out – because that may put the patient's life in danger. Psychiatrist must rule out from the chart review, **medical emergency conditions** where respiratory distress with autonomic hyperactivity or non-specific chest discomfort, palpitation with accompanying worries and anxiety may often be the presentation, like –

- Exacerbation of chronic respiratory pathologies,
- Myocardial infarction, myocarditis, cardiac arrythmias
- pulmonary embolism, tension pneumo-thorax
- anaphylactic condition with respiratory distress
- occult severe blood loss (like ruptured ectopic pregnancy)
- metabolic acidosis-alkalosis in a known patient of diabetes or kidney disease
- catecholamine excess condition like pheochromocytoma etc.

Psychiatrist should discuss those possibilities with the attending physician and check whether they have been ruled out for immediate cause or kept in future plan – before proceeding further towards assessment of any psychiatric conditions.

Psychiatrists should also rule out:

- Any history of acute **substance** intoxication (most commonly cannabis and cocaine)
- Sudden withdrawal (in chronic heavy opioid use)
- Surreptitious attempt of deaddiction (like disulfiram reaction in alcoholics or oral opioid antagonist in opioid dependence).

Next on general observation, patient's behavior and motor activities should be closely noted, followed by interview of the patient. There may be following possibilities:

- If there is restlessness, 'looking to escape' out of the place with 'as if an air-hunger' – and on interview patient reports 'bolt from the blue' appearance of anxiety symptoms which gradually 'increased in a crescendo manner' over minutes to a peak where appears a 'sense of impending doom' – that raises possibility of panic attacks. In case of **panic attack**, enquire whether it is an isolated attack or occurring frequently over last one month to fulfill panic disorder.
- At times, there may be hyperventilation with topsy-turvy movements and verbal responses from groaning to variable utterances – this raises the possibility of **conversion symptoms** or may be **focal seizures of frontal lobe origin**.
- In **focal seizures simulating panic attack**, there would be a ball like upward discomfort from epigastric region to chest with respiratory distress, hyperventilation, swallowing and an unexplainable discomfort in head and inability to communicate the distress to surrounding people – lasting for few minutes – proceeding to either gradual recovery or passing into a stage of altered posturing with variable tone of the body with non-responsiveness for some time and associated amnesia on awakening – this suggests focal seizure of **usually temporal lobe origin** with or without generalization – which should be evaluated by any neurologist available at that point or later

After initial assessment and their relevant management, plan for further detailed work-up in psychiatry ward as the case may be:

- In case of panic attack or conversion symptoms, other associated conditions to rule out:
  - Depression and other mood disorders, GAD, phobia etc.
  - Acute stress-trauma (post-traumatic-stress-disorder or adjustment disorder)
  - Personality disorders
  - May use screening tools like, BPHQ, BPRS, PHQ-9, GAD-7

- **Certain acute sensory-motor presentations considered as 'functional' or 'medically unexplained'**

While attending to this kind of cases on referral, the CL-psychiatrist must not get biased towards dissociative-conversion symptoms from the outset, that may lead to overlooking of many underlying organic conditions. Following are the usual presentations and their organic versus psychiatric possibilities:

- **Diagnostic confusion between seizure versus non-epileptic-psychogenic-events (NEPE)** -this will be covered in subsequent chapter of psychiatric disorders in epilepsy

- **Acute onset motor disturbances including gait, speech, abnormal involuntary movements** [14,19,20,21]

	Organic	Psychogenic
Sudden Gait difficulties	Sudden gait difficulties with organic etiology – **rare**. History of **fever** raises suspicion of acute post-infection demyelinating polyneuropathy (**Guillain Barre syndrome)** Any ongoing clinical state suggestive of: ▪ **Nutritional (thiamin) deficiency** ▪ Hyponatremia and subsequent rapid correction - **osmotic demyelination** ▪ Toxic condition - **Neuro-lathyrism** which may present like poliomyelitis.	Sudden appearance is a suspicion for psychological origin, but never a surety Usually, no definitive gait pattern or difficulties – gait appears chaotic in nature – appears as if would fall without support – but usually no fall or injury – **astasia-abasia** -may be with complain of extreme pain and attention seeking behavior (but not the classical antalgic pattern for any focal lesion) History of any **fall and injury** on head due to movement difficulties – very much **unlikely** to be psychogenic.

	▪ Intoxication or withdrawal of substances - particularly **alcohol** ▪ Loading dose or rapid escalation of **psychotropics** (particularly lithium, carbamazepine, valproate, low potency antipsychotics Must carry out – Detailed neurological examination of pyramidal and extra-pyramidal system, cerebellum, posterior column, ocular gaze, frontal lobe, bladder-bowel control etc. **Postural hypotension** and vertigo to be ruled out.	Neurological examination either normal or inconsistent.
Sudden Speech difficulties	To rule out non-fluent **aphasia**, ability of comprehension, word naming, repetition to be tested. In case of sudden aphasia – stroke, TIA, postictal state to rule out. In true **aphonia** patient is unable to cough and whisper with strain and stridor In mutism with catatonia like presentation and associated fever-rigidity infective and other metabolic **encephalopathy** to rule out	Conversions usually presents with acute **aphonia** rather than aphasia In **psychogenic aphonia** patient has no dysphagia or stridor and either refuses to cough or cough normally; may whisper without strain In mutism, other features of **catatonia** (disturbance of tone, waxy flexibility, maintenance of posturing, automatic obedience) to rule out

Sudden Involuntary Movements and Posture	Acute onset **drug-induced dystonia** is a common condition on exposure to typical antipsychotics or injectable antiemetic like metoclopramide. Sudden involuntary movements are rare -may be **focal seizures;** sudden choreiform movements in fever with autoimmune condition (**Rheumatic fever), pregnancy**, **non-ketotic hyperosmolar hyperglycemia**, or drug induced tremor etc In case of sudden appearance of abnormal movements **during sleep** initiation or middle of the sleep with abnormal behaviors and vocalization – raise suspicion of RLS (restless leg syndrome) or REM-BD (behavior disorder associated with rapid eye movement sleep)	Unlike dystonia, psychogenic posturing is not painful. **Psychogenic posturing** to be differentiated from catatonia by other associated features Psychogenic abnormal movements get reduced on distraction, have chaotic pattern – settles with sleep– but should be confirmed by sleep electrophysiology whether the patient was actually sleeping or not
Presentation with gross reduction in spontaneous movements and reactivity – **Stupor**	History of: o Head injury - Fall o Remaining in closed room with source of fire -Carbon monoxide poisoning o Substances Intoxication o Fever – Vomiting – Convulsion o Known Diabetes –Insulin treatment o Chronic Liver, Kidney disease o Parkinsonism o Chance of electrolyte imbalance Must rule out psychotropic exposure and life-threatening Neuroleptic Malignant Syndrome (**NMS)** Examination of ➢ Pulse-BP – Respiration ➢ Pupil - Planter ➢ Glasgow Coma Scale ➢ Muscle tone -jerks-power ➢ Focal lateralizing signs ➢ Signs of meningeal irritation ➢ Brainstem reflexes	Presentation of Stuporous condition with history of antipsychotic exposure is the trickiest condition between NMS and psychogenic presentation **Catatonia** to be established by motoric signs of altered muscle tone like rigidity-lead-pipe/gegenhalten- resistance, waxy flexibility; or altered responses like negativism, automatic/passive obedience, grasp reflex, echolalia-echopraxia etc (vide **Busch Francis Catatonia scale)**[22] Catatonia my at time present with fever (**Lethal catatonia** -starts with extreme excitement – progresses with exhaustion and fever) **Differentiation Lethal Catatonia vs NMS** o Autonomic instability commoner in NMS

	Investigation of - ➢ Capillary Blood Glucose (CBG) ➢ Arterial Blood gas Analysis (ABG) ➢ Cerebral Imaging ➢ Serum electrolyte, urea, creatinine Liver function test with serum-ammonia ➢ Serum CPK (creatinine phosphokinase) and Cell count (CBC) ➢ CSF study To be kept in mind: ➢ Anoxic and metabolic stupor is a diagnostic problem ➢ Psychogenic stupor is a rarity.	o In Lethal catatonia Excitement -Exhaustion - fever o In NMS, Rigidity -fever **Dissociative stupor** o Rare o Rule out organic conditions, NMS, catatonia o Here muscle tone usually normal or low o A common test of **passive raising of hand over face and letting it fall** usually does not fall on face in dissociation.

- **Acute onset sensory deficits like vision, hearing, somato-sensory disturbances** **[14,19,20,21]**

	Organic	**Psychogenic**
Visual Loss	Detailed ophthalmological and neurological workup (Visual Evoked Potential) is a must **Optokinetic Nystagmus** is often a differentiating feature for organic lesion Clinical conditions like hemineglect, alexia without agraphia, **Balint's syndrome** (simultanagnosia – missing the forest for the wood; oculomotor apraxia – inability to fix the eyes at the intended area; optic ataxia – inability to move the hand to a specific object using vision) etc. may well appear psychogenic, but actually are result of stroke at non-dominant or bilateral parietal and occipital lobes.	**Nonorganic visual loss (NOVL)**[23] – in either visual acuity or field loss – should be a diagnosis of exclusion after detailed ophthalmological evaluation. **Altered test of proprioception** in a patient with complaints of visual difficulty is a strong suspicion of psychogenic condition, as that does not involve any role of vision, but does not rule out organic lesion at sensory parietal cortex. Recognition of NOVL as either **conversion or malingering** is more of circumstantial (in situations of conflict with law) on the basis of moral accusation rather than medical.

	On the contrary in **Anton syndrome** there may be visual loss but patient remains unaware of it (bilateral occipital lobe damage - stroke)	
Hearing loss	Detailed examination of hearing pathology is a must, but some of the audiometry tests reports may become unreliable because of improper response of patients, where attention-distraction procedure would be needed	Complain of sudden complete hearing loss with no restriction of activities and la belle indifference affect may raise suspicion of psychogenic origin. Patients usually show no distress or effort to listen what is being said to him or her.
Cutaneous sensory disturbances with dysthesia, numbness or pain	In acute neuropathy or peripheral, spinal or cranial nerves there would specific dermatomal rule of distribution. Reflex function for the region is helpful In case of plexopathy an wide area of involvement like complete limb with both sensory and motor involvement Variable and fleeting presentation of dysthesia – numbness, pin pricking, electrical sensation in different unrelated areas – may be tricky – needs to rule out MS (**multiple sclerosis**)	Localization of pain is vague No motor involvement which may be associated with neuropathy Variable emotional expression – from marked restlessness, anxiety, crying out for help in case of pain to apparent la-belle -indifference in complain of cutaneous anesthesia Preceding psychological stressor may raise suspicion but organicity must be ruled out

Despite all the differences enumerated in above tables, it is difficult on a single clinical contact to differentiate these conditions with certainty. So, treating team at emergency should be

communicated about the plan for further evaluation in detail by both neurologist and psychiatrist.

II. Psychiatric assessment at ICU:

In critical care units, most common cause of psychiatric referral is for confusion with behavioral abnormalities which they colloquially refer as 'ICU-psychosis'. These conditions are actually delirium which should be assessed as mentioned earlier. Regarding causes of delirium, in case of ICU set up one important issue is absence of exposure to natural light which may deprive the patient from awareness of day-night change. Primary care personnel at ICU may be trained with screening tool **RASS**[24](Richmond Agitation Sedation Scale) **CAM-ICU**[25](Confusion Assessment Methods -ICU)] for quick screening of delirium. In ICU, hypo-active delirium is often seen which should be differentiated from NCSE by EEG and other neurological evaluation.

III. Psychiatric Assessment at non-emergency and chronic care units of different specialties:

In these settings, CL-psychiatry services operate both in collaborative and referral model for both admitted as-well-as OPD patients. Collaborative medical-n-mental health care are quite common in different superspeciality units like neurology, oncology, geriatric medicines while referral model in multidisciplinary hospitals. Subsequent chapters in this CPG will deal with assessment of the particular conditions encountered in different specialties. Here we would give a general outline.

Among all medical specialties across all ages, **stress-anxiety-depression and somatic distress** are the most common psychiatric symptoms or morbidities among those patients.

Assessment of Depression: While the prevalence of depression in community ranges around 10% it goes up to 30% in different medical units which significantly impact the overall outcome.[14] For early recognition of depression, apart from empathic interview regarding one's prevailing mood, pleasurability and vegetative functions, there can be quick and effective use of following tools:

- **PHQ-9**[5] – Gold-standard screening tool for depression in most of the settings - part of PRIME-MD-PHQ or BPHQ -with only 9 self-rated question- also used for rating depression in primary care settings
- **HADS**[26] (Hospital Anxiety Depression Scale)- is another important tool commonly employed in hospital setting for screening of both anxiety and depression.

Apart from these two tools, there are certain **age customized tools** for screening of depression:

- **GDS**[27] (Geriatric Depression Rating Scale) - Considering the age variation, both screening and rating of depression in geriatric population is commonly done by GDS. This self-rated tool is not applicable for elderly population with significant cognitive decline or dementia, who fail to respond properly.

- **CPMS**[28] (Childhood Psychopathology Measurement Schedule) - Depressive symptoms are also common in childhood population in hospital settings suffering from chronic morbidities like thalassemia, nephrotic syndrome or malignancy. They can be screened with CPMS and subsequently rated with **CDRS**[29](Children's Depression Rating Scale)

Two medical conditions are worth mentioning which merit specific screening tool for depression:

- **SADQ**[30] (Stroke Aphasic Depression Questionnaire) – Nearly one-third of patients of stroke suffer from aphasia who find it difficult to understand and respond to the standard screening tool questionnaire. This scale, based on the response of the attendant, is of immense importance in recognition and monitoring of depression in these patients of stroke with aphasia.
- **CSDD**[31] (Cornell Scale for Depression in dementia) - Depression is a very common comorbidity in dementia where the presentation is different from other depressed patients and there may be co-occurring apathy which masks the usual presentation of depression. This tool is very important for this population of patients.

In all the depressed patients any **Suicidal intent** must be screened meticulously as depicted earlier.

Apart from depression, anxiety disorders are also common presentation in medical setting in 20-30% patients,[14] which either co-occur with different medical morbidities or may mimic complaints of respiratory and chest discomfort. **Screening tools for quick recognition of anxiety disorders:**

- Anxiety questionnaire of – **BPHQ**[4] and **HADS**[26]
- **GAD7**[6] (Generalized Anxiety Disorder -7 item)
- **PDSR**[32] (Panic Disorder Self Report) -An effective screening tool for panic disorder yet to be translated and used in Indian studies

Variable and multiple somatic complaints is another important issue with which patients frequently visit different departments in hospital setting, which cause significant impairment and health-care utilization. In these patients, depression is to be ruled out first by above appropriate screening tools because depression often presents with somatic distress and untreated depression causes serious health hazards. After ruling out depression, following tools can be used for assessment of patients with **Somatic distress:**

- **PHQ-15**[7] (Patient Health Questionnaire -15 items): A self-rated screening tool developed from PRIME-MD-PHQ for recognition and severity of somatic symptoms
- **SSS8**[33] (Somatic Symptoms Scale 8 item): This is another self-rated tool based on PHQ-15, which divides the symptoms burden questionnaire into 4 domains -cardio-pulmonary, gastro-intestinal, pain and general. However, Indian translation or studies not available.
- **IBQ**[34] (Illness Behavior Questionnaire) – Apart from subjective distress another important aspect of these complaints is healthcare utilization. This tool gives an idea about this health-care seeking behaviors.

Chronic and serious medical morbidities along with hospitalization increase stress of an individual which in a vicious cycle further worsen the outcome of those illnesses. To cope with that stress, one should have resilience which in turn predict good outcome. **Perceived stress** and **Resilience** can be screened with tools like -

- **PSS[35]** (Perceived Stress Scale)
- **CD-RISC[36]** (Connor Davidson Resilience Scale)

These tools are particularly useful in specialties like oncology, trauma, burn, patients waiting for transplant etc

Apart from the commonly encountered internalizing symptoms, there may be exacerbation of already existing or newly appearing **psychotic conditions and their related agitation, aggression** which can be most effectively screened as-well-as rated by **BPRS[10]** (Brief Psychiatric Rating Scale).

Screening for cognitive decline should also be done particularly in elderly population and patients with chronic neurological illnesses – like epilepsy, movement disorders, stroke, head injury, HAND (HIV associated neurological illnesses); post-Covid patients, etc. They can be done with different standardized tools like **MMSE[37]** (Mini Mental State Examination) **and MoCA[38]** (Montreal Cognitive Assessment test), both of which has validated Hindi version – **H-MSE[39]** and **H-MoCA[40];** or neuropsychological batteries developed by NIMHANS[41] or PGI, Chandigarh[42]. Another screening tool has been developed in Kolkata, West Bengal in Bengali language to screen for non-demented early cognitive impairment subjects from urban community which is known as **KCSB** (Kolkata Cognitive Screening Battery) which also includes **B-MSE** (Bengali-Mental State Examination).[43] This tool has a corresponding Hindi version applicable for rural Hindi-speaking population of India.[44]

In case of diagnosed **dementia**, behavioral and psychological symptoms (**BPSD**) can be assessed by **NPI[45]** (Neuropsychiatric Inventory), BPRS, CSDD, Apathy Evaluation Scale etc.

There can be many more specific psychiatric issues and their customized screening and evaluation tools associated with different medical units which would be discussed in subsequent chapters.

IV. Assessment of need for medical-work-up in patients undergoing treatment in psychiatry units

- Suspicion and assessment of **tell-tale signs of organicity** in patients presented to psychiatric units, some notable examples [19,20]
    - Psychosis – confusion, seizure, subacute onset– autoimmune encephalitis
    - Depression – weight loss, severe pain – multiple myeloma
    - Depression – anorexia, nausea, pain abdomen – gastric, pancreatic carcinoma
    - Depression/Anxiety – panic attack like autonomic features, flushing – paraneoplastic conditions in lung carcinoma in elderly or Pheochromocytoma in young
    - Late onset mood disorder – neuroleptic sensitivity, subtle movement disorders – degenerative conditions of brain

- Apparent dissociative conditions – localization related epilepsy or non-motoric vascular lesions of brain – Balint's/Gerstman/Anton syndrome etc…

- Assessment for **medical comorbidities** and **psychotropic-induced medical complications** can follow Maudsley practice guidelines for physical health conditions in psychiatry[46]. The mantra is, regular medically vigilant clinical (general and systemic) examination coupled with investigations –- details of which will be dealt in subsequent chapters.

V. Multidisciplinary Assessment at medical boards

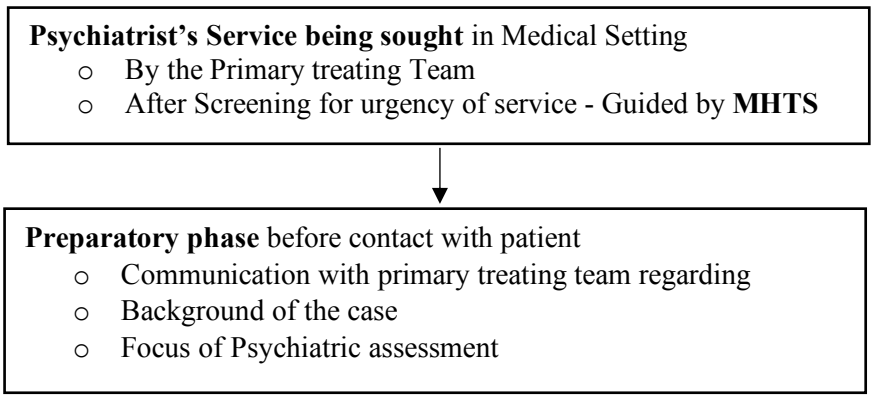
Psychiatrists often act as member in a multidisciplinary medical board for assessment of following conditions:

- Physical and mental state assessment of a victim of sexual assault particularly children – immediate stress, trauma and subsequent PTSD, depression
- Examination of children in conflict with law (CCL) referred by Juvenile-Justice-Board (JJB) to assess their capacity to understand the nature and consequence of their acts and their need for protection and care

NIMHANS – child and adolescent department of psychiatry has detailed guidelines on child protection issues which can be looked into their designated website https://www.nimhanschildproject.in

- Assessment of fitness or capacity of a person to pursue certain works after long absenteeism, or giving testaments or stand trial in legal cases in terms of physical and mental abilities – like cognitive functions and major psychiatric-disorders like psychosis, unremitting mood disorders or OCD. These can be assessed by scrutiny of previous treatment papers, current MSE, psychometric assessment, application of appropriate screening tools and rating scales
- If the above conditions become unremitting, persistent with significant deterioration in quality-of-life and psycho-social-impairment – the patients qualify for **disability certificate** after assessment with **IDEAS** (Indian Disability Evaluation and Assessment Scale).[47]
- Another important issue in this board is to assess for malingering. During skillful interview, 'too perfect' a tale almost taken out of diagnostic criteria, or too vague or unrealistic tale – raise suspicion of malingering. There is no fixed and authentic protocol to deal such cases. Before giving final opinion, the incumbent should be observed regularly over next 6-8 weeks with serial MSE, application with screening tools and application of psychometry.

Psychiatric assessment in CL-setting in a flow-chart:



First contact with the Patient and Informant

- Introduction as Psychiatrist
- Explanation of Reason for Psychiatric Assessment
- Rapport Building and ensure optimum privacy

Detailed **Interview and History Taking**

- Start with open narrative of patient's current distress
- Should never be biased towards psychiatric origin of the problem
- Enquire vegetative functions, Internalizing and Externalizing symptoms
- Any substance intake – if so – in details
- Any decline in cognitive functions particularly in elderly
- Patient's background Intelligence level, psycho-social position
- Any ongoing Stressor
- Any history of Suicide attempt in patient and close relative
- Any risk of harm to self and others
- Any Medicolegal issues
- Any mal-adjustment with hospital and its reason

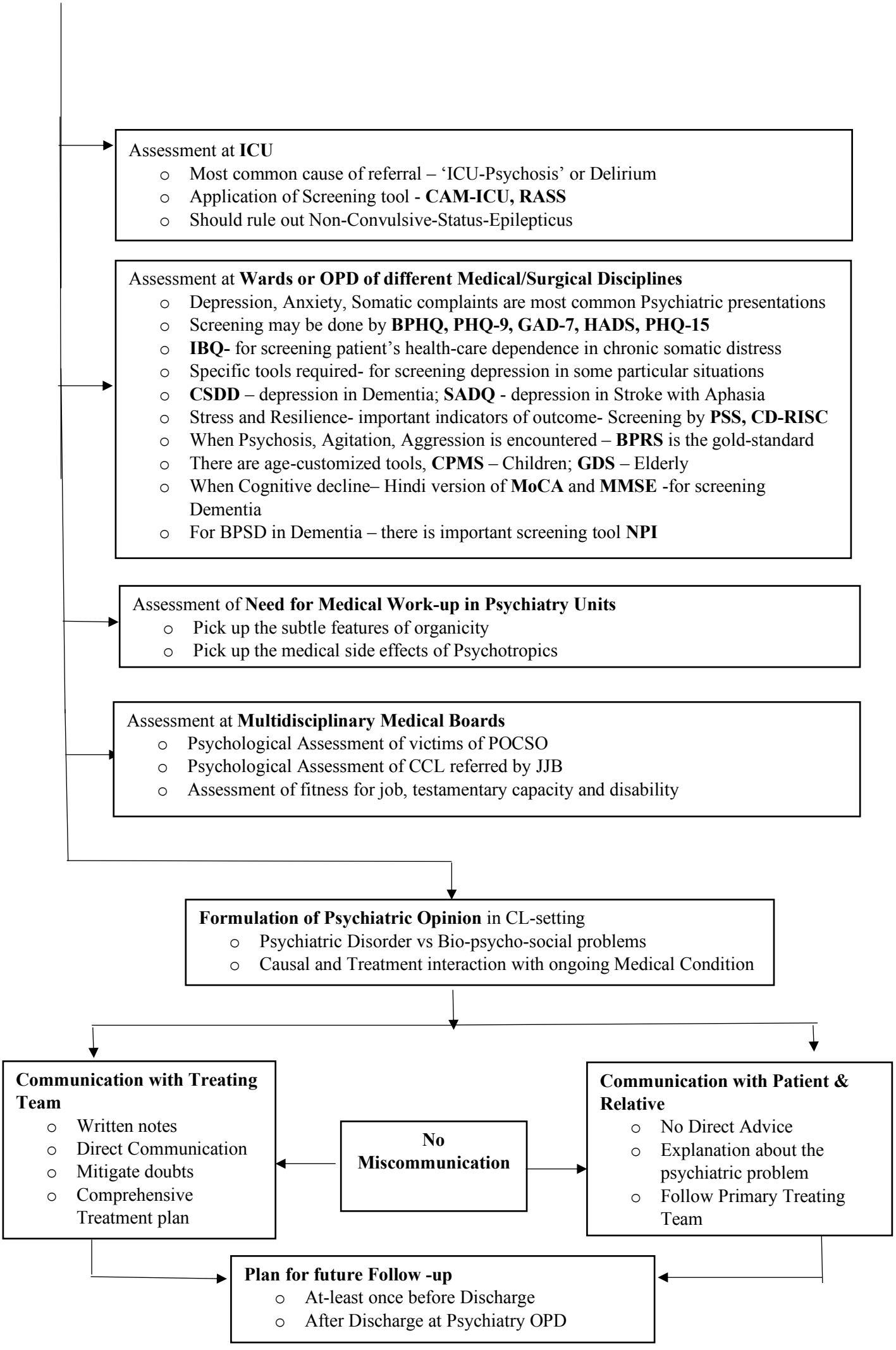
Mental Status Examination

- Start with Consciousness, attention, orientation
- Then conceptual organization from speech
- Affect and related anxiety, somatic complaints
- Thought and Perception suggestive of psychosis
- Bedside quick cognitive assessment if indicated
- Assessment of risk of suicidality or harm to others
- Patient's insight regarding ongoing Medical and Psychiatric problem/illness

Customized Assessment in Particular settings

Assessment at **ER units**

- Always ensure undiagnosed medical issues are not missed
- Confusion with Behavior abnormality is the most common cause for referral
- First rule out Delirium -screening tool **NEECHAM** may be used
- Substance intoxication and withdrawal are quite common -use **AUDIT** for alcohol use
- Disorganized psychosis comes next - may be screened by BPRS
- In Panic attack like states – Medical emergency to rule out first -followed by **BPHQ**
- In 'Functional Neurological Presentations' – Detailed evaluation of Organicity
- Dissociative states are always diagnosis of exclusion
- In Suicidal attempts – detailed evaluation after initial stabilization- may apply **C-SSRS**


Assessment at **ICU**
Most common cause of referral – 'ICU-Psychosis' or Delirium
Application of Screening tool - **CAM-ICU, RASS**
Should rule out Non-Convulsive-Status-Epilepticus
Assessment at **Wards or OPD of different Medical/Surgical Disciplines**
Depression, Anxiety, Somatic complaints are most common Psychiatric presentations
Screening may be done by **BPHQ, PHQ-9, GAD-7, HADS, PHQ-15**
IBQ- for screening patient's health-care dependence in chronic somatic distress
Specific tools required- for screening depression in some particular situations
CSDD – depression in Dementia; **SADQ** - depression in Stroke with Aphasia
Stress and Resilience- important indicators of outcome- Screening by **PSS, CD-RISC**
When Psychosis, Agitation, Aggression is encountered – **BPRS** is the gold-standard
There are age-customized tools, **CPMS** – Children; **GDS** – Elderly
When Cognitive decline– Hindi version of **MoCA** and **MMSE** -for screening Dementia
For BPSD in Dementia – there is important screening tool **NPI**
Assessment of **Need for Medical Work-up in Psychiatry Units**
Pick up the subtle features of organicity
Pick up the medical side effects of Psychotropics
Assessment at **Multidisciplinary Medical Boards**
Psychological Assessment of victims of POCSO
Psychological Assessment of CCL referred by JJB
Assessment of fitness for job, testamentary capacity and disability
Formulation of Psychiatric Opinion in CL-setting
Psychiatric Disorder vs Bio-psycho-social problems
Causal and Treatment interaction with ongoing Medical Condition
Communication with Treating Team
Written notes
Direct Communication
Mitigate doubts
Comprehensive Treatment plan
No Miscommunication
Communication with Patient & Relative
No Direct Advice
Explanation about the psychiatric problem
Follow Primary Treating Team
Plan for future Follow -up
At-least once before Discharge
After Discharge at Psychiatry OPD

Appendix of Psychiatric-Assessment-Tools in CL-settings & Indian Studies

(In Alphabetical order)

Name of the Tool	Focus of Assessment	Indian Validation & Adaptation	Source of Availability
AUDIT[15] (Alcohol Use Disorder Identification Test)	▪ WHO Guideline ▪ For Primary Health Care ▪ Screening for degree of problematic alcohol use – Hazardous-Harmful - Dependence ▪ 10 questions by interviewer over few minutes ▪ Also contain information on associated Health Hazards and Brief Intervention	Translation and validation of the tool in Hindi[48] Studies have been done to validate the tool both North Indian[49] and South Indian[50] population.	Manual https://apps.who.int/iris/handle/10665/67205
Beck's SSI[17] (Scale for Suicidal Ideation)	▪ Interviewer rated 21-item scale -scoring on 19 items ▪ 5 items for screening ▪ If positive 14 items for severity ▪ Current Intensity on the day of interview ▪ Two major dimensions of Suicidal Desire and Preparation ▪ Total time about 5 minutes	Used in Indian study on patients admitted with suicidal attempt in a tertiary care general hospital[51]	Copyright 1979 by the American Psychological Association, Inc. 0022-006X/79/4702-0343$00,75 (Manual sold by Pearson Assessment Publication)
BPHQ[4] (Brief-Patient Health Questionnaire)	▪ Self-rated 2-page questionnaire ▪ Quick and easy to apply in primary care setting ▪ Adapted from PRIME-MD-PHQ ▪ Targets depression-anxiety-panic- somatic complaints-stress-trauma-	Adapted and translated in 11 Indian Languages Standardized with DSM IV Depression Criteria in Indian study[52]	Indian Translation-Copyright Pfizer India and PRIME-MD study group with reference to Indian study
BPRS[10] (Brief Psychiatric Rating Scale)	▪ Interviewer rated questionnaire ▪ Gold standard for screening and rating of wide range of symptoms including psychosis, agitation, catatonia, anxiety, mood, self-harm ▪ 24 items – 0-7 scoring ▪ 20-30 mins	Applied in innumerable Indian studies Corroborate with severity and urgency of psychiatric assessment as found in Indian study[9]	Manual https://usermanual.wiki/Pdf/Brief20Psychiatric20Rating20Scale20BPRS20Instructions.1342467641/view

CAM-ICU[25] (Confusion Assessment Methods - ICU)	▪ Screening tool for delirium in ICU by Physician, Nurses ▪ Start with **RASS** (Richmond Agitation Sedation Scale) for Arousal then progress further ▪ Assess presence, severity and fluctuation ▪ Both verbal and non-verbal (ventilated patient) ▪ Non-verbal ratings have high specificity but low sensitivity and low inter-rater reliability	Indian study on incidence and outcome of delirium in non-intubated ICU patients in a tertiary care private hospital with this tool[53]	Manual http://tetaf.org/wp-content/uploads/2016/03/CAM_ICU_training.pdf
CDRS[29] (Childhood depression Rating Scale)	▪ 17-item Clinician rated ▪ Children of age 6-12 yrs (may be extended up to 18) ▪ Validated in Medical settings ▪ A revised version CDRS-R is there for extended range of severity scoring	Indian study has been done in CMC Vellore to validate CDRS-R for adolescents in in primary care[54]	Manual http://www.scalesandmeasures.net/files/files/Childrens%20Depression%20Rating%20Scale%20Revised%20(1995).pdf
CPMS[28] (Childhood Psychopathology Measurement Schedule)	▪ Clinician rated Screening tool for 4-14 yrs ▪ Total 85-item schedule with 8 factorially derived domains of syndromic psychopathology -like low intelligence, conduct, anxiety, depression, psychosis etc ▪ May screen for individual domain or overall score	Indian tool developed at PGI Chandigarh Based on CBCL (Childhood Behavior Checklist)	Scale with Author's Citation
CD-RISC[35] (Connor Davidson Resilience Scale)	▪ A measure of stress coping ▪ Applied in wide range of setting including Hospitals ▪ Important indicator of improvement for patients of trauma, stress of serious illness ▪ Interviewer assisted self-rated questionnaire of 10 or 25 item – quick to apply	Psychometric evaluation of the scale has been done in studies on Indian student population[55] No Indian translation found	Manual http://www.connordavidson-resiliencescale.com/CD-RISC%20Manual%2008-19-18.pdf due reference to author

CSDD[30] (Cornell Scale for Depression in Dementia)	▪ Interviewer rated scale with interview of both patient and informant ▪ Screening Tool with multiple domains comprising 19 items ▪ About 20 mins interview ▪ Final score on overall impression of Clinician ▪ More valid and commonly used than GDS in BPSD studies	Indian studies with CSDD not found	Manual https://dementiaresearch.org.au/wp-content/uploads/2016/06/CSDD.pdf due reference to author
C-SSRS[18] (Columbia-Suicide Severity Rating scale)	▪ Interviewer rated ▪ Two screening domains - Suicidal ideation and Behavior ▪ Two rating domains - Intensity of ideation and lethality of behavior ▪ Also includes NSSI ▪ More extended domain – quick to apply but scoring is complicated	It has Translated version in 7 Indian languages -for free use under Columbia Lighthouse Project for suicide prevention to contact posnerk@nyspi.columbia.edu No Indian study could be found	Manual https://suicidepreventionlifeline.org/wp-content/uploads/2016/09/Suicide-Risk-Assessment-C-SSRS-Lifeline-Version-2014.pdf
GAD-7[6] (Generalized Anxiety Disorder -7 item questionnaire)	▪ 7-item both self-report and interviewer-administered questionnaire for screening of GAD ▪ Developed from PRIME-MD-PHQ ▪ Matches clinician's diagnosis by DSMIV	Study done on suitability of this tool and PHQ9 on large sample of Indian patients under diabetes care[56]	Hindi translated version is available with Pfizer India website
GDS[27] (Geriatric Depression Rating Scale)	▪ Self-rated screening tool long (30 item), short (15 item) -Yes/No response ▪ Extensively used in geriatric medical setting except dementia ▪ Response 'No' on Question 1,5,7,11,13 & 'Yes' on rest 10 question -gets score 1 ▪ Score 5 probable depression, 10 definite ▪ Also used as rating of depression -5-8 mild; 9-11 moderate; 12-15 severe	Validated Hindi Translated tool H-GDS[57] Also available in other language, like Bengali[43]	Original scale manual https://hign.org/sites/default/files/2020-06/Try_This_General_Assessment_4.pdf Indian version with Author
HADS[26] (Hospital Anxiety	▪ Separate Anxiety and Depression Screening questionnaire	Study on cancer patients with Malayalam version[58]	Officially distributed by https://eprovide.mapi-

Depression Scale)	▪ 7 questions in both group with scoring 0-3 for each ▪ Cut-off score >10-definite, 8-10-doubtful ▪ 4-5 min self-rated ▪ Developed for hospital setting – like anxiety for syringe		trust.org/instruments/hospital-anxiety-and-depression-scale#languages
IBQ[33] (Illness Behavior Questionnaire)	▪ 62 self-rated Yes/No questions ▪ Patient's attitudes, ideas, affects, and attributions in relation to illness ▪ Delineation between care-seeking vs assuming self-responsibility	Indian study did translation and Validation of this tool in Hindi Language[59]	Questionnaire at https://psychology.okstate.edu/faculty/jgrice/psyc5314/ibq.pdf
KCSB[43] (Kolkata Cognitive Screening Battery)	▪ Screening of mild cognitive impairment or decline in Bengali ▪ Initially obtained normative data on urban elderly population ▪ Contains B-MSE, Verbal, Visuo-constructional and Memory items	Validated with Hindi version in rural Hindi-speaking population of Ballabgarh, North-India[44]	Tool and the cut-off score are given in appendix of original article
MMSE[36] (Mini Mental State Examination)	▪ Most commonly employed tool for cognitive screening ▪ 12-item with 30 score -sets cut-off for dementia (<20) vs Mild cognitive impairment (<25) ▪ Remained gold standard for 5 decades	Translated and Validated Hindi tool - HMSE[38] for Rural, illiterate population Pilot study[60] done on urban elderly-but validity inconclusive on illiterate people	MMSE copyrighted for all use in 2000 to Psychological Assessment Resources (PAR) HMSE in public domain with Author citation
MoCA[37] (Montreal Cognitive Assessment test)	▪ Newer screening tool with domain specific cognitive-assessment ▪ More sensitive for Mild impairment ▪ Gives importance to educational status of the patient in scoring ▪ Pictorial representation	Translated and validated in Hindi - H-MoCA[39]	Manual https://geriatrictoolkit.missouri.edu/cog/MoCA-8.3-English-Instructions-2018-02.pdf

NEECHAM[13] (Neelon and Champagne) Confusion Scale	▪ Delirium screening instrument in medical, surgical wards and also ICU ▪ For nurses – takes 10 mins ▪ 3 subscales -cognitive functions/ Behavior/Physiological state (Temperature, Respiration)	Indian study was conducted to corroborate NEECHAM confusion scale and **RASS** among ICU patients[61]	Manual https://www.mnhospitals.org/Portals/0/Documents/patientsafety/Delirium/Neecham%20Confusion%20Tool.pdf
NPI[45] (Neuropsychiatry Inventory),	▪ Tool for assessing broad array of 12 domains of psychopathology in BPSD over last month ▪ Informant's self-rated questionnaire- Yes/No ▪ If 'Yes' – the rating of severity 0-3 and rating of Distress/Care-giver burden 0-5 in each domain ▪ Average time 5 min	Indian study has been done with NPI to compare BPSD in Alzheimer's, Vascular and bvFT dementia[62]	Manual https://download.lww.com/wolterskluwer_vitalstream_com/permalink/cont/a/cont_21_3_2015_02_26_kaufer_2015-10_sdc2.pdf
PHQ-9[5] (9-item Patient Health Questionnaire for depression)	▪ Quick self-rated tool ▪ 9 items -each scoring 0 (not at all) –to- 3(nearly every day) over last 2 weeks ▪ Cut off score is variable 7-15, most common being 10 ▪ Also used as rating scale in primary care settings – with score 5,10,15,20 indicating mild, moderate, moderately and severe depression	Translated in 11 Indian languages Plenty of Indian studies in different languages Indian study[63] with Malayalam language found cut-off score as 9	Indian version available with Pfizer India Website
PHQ-15[7] (Patient Health Questionnaire -15 items)	▪ Brief -Interviewer assisted -self rated tool for somatic complaints ▪ Each item score 0 (not bothered) -2 (highly bothered) over last 4 weks ▪ 5,10,15 -cut-off for low-medium-severe ▪ Applicable in multiple health settings -general medicine to obstetrics	Indian study[64] used PHQ-15 for somatic complaints in depression and dementia	Free at file:///C:/Users/Ray/Downloads/PHQ_15%20(1).pdf
PSS[34] (Perceived Stress Scale)	▪ Interviewer assisted self-rated tool ▪ Quick to apply 10 questions with 0-4 score ▪ Screen stress over last 1 month	No Indian version available with the designated website of Sheldon Cohen	Questionnaire and Scoring https://das.nh.gov/wellness/docs/percieve

	▪ Scores beyond 20 found to be associated with health hazards	One Indian study[65] on 37 Medical personnel for validation of Bengali translation of PSS-10	d%20stress%20scale.pdf
SADQ[29] (Stroke Aphasic Depressive Questionnaire)	▪ For clients with significant aphasia (minimum understanding and response) ▪ Interviewer assisted ratings of observation by caregiver ▪ Initial 21-item, later revised 10 item and for Hospital use to be rated by hospital staff ▪ Few minutes Screening tool with cut-off score around 14	Translation and Adaptation in Hindi Language done[66] for SADQ-10	Details of scale https://strokengine.ca/en/assessments/stroke-aphasic-depression-questionnaire-sadq/

(All websites were searched on 31.10.21;
Always use the scales with citation of Original-Article and the Source
Check for the updated copyright status)

Summary

- For psychiatric assessment in CL-settings there should be a preparatory phase and a distinct way of introduction and communication with patients compared to individual clinical practice
- Focus of assessment is guided by the need of the primary treating team for better management of patient, as well as to relieve the strain perceived by them to handle the mal-adaptive behaviors of patient
- Apart from skillful interview and MSE, multiple screening tools are of utmost importance
- In CL-psychiatry practice, psychiatrists should have a sound medical knowledge parallel to their knowledge in psychiatry for proper assessment of the condition
- The three 'C' - conceptualization, communication and control in CL-psychiatry practice holds some definite uniqueness than individual clinical practice

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Overview of Practice of Consultation - Liaison Psychiatry

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Introduction

The first revolution in psychiatry is generally acknowledged to be the unchaining and moral treatment offered to mental patients. The second revolution was heralded by the invention of electroconvulsive therapy (ECT). It was the first effective and easily feasible treatment option for a variety of mental illnesses. Another leap for psychiatry was the introduction of psychotropic agents, chlorpromazine to be particular in the year 1952 and the later discovery of a series of antidepressants, antianxiety, antipsychotic and other neuroleptic drugs. It changed the face of psychiatry forever and allowed domiciliary treatment. This is generally regarded the third revolution of psychiatry and combined with the treatment of the mentally ill outside the four walls of the mental hospital has revolutionized the outcome of mental illnesses.
Addressing comorbidities of mental illnesses with chronic physical illnesses will be the fourth revolution in psychiatry. Mind and body are inseparable there is a bidirectional relationship between psyche and soma, each influencing the other. Psychological factors must be taken into account when considering all disease states. Physical diseases have a large overlap with mental disorders. All physical illnesses and their management cause a psychological reaction. This may or may not reach morbid levels, similarly mental illnesses and stress predispose to a large variety of physical illnesses. A bidirectional relationship has been established and the evidence grows by the day. Plausible biochemical explanations are appearing at an astonishing rate. We are all aware of the neurochemical response, immune response and endocrine response to stress.

Almost 1/5th of the global burden of disease is attributed to neuropsychiatric disorders. Most significantly common mental disorders such as anxiety, mood disorders and substance use disorders contribute to overall mental health burden. Most of the patients with these common and mild form of disease is seen by non mental health professionals ,especially medical settings .Moreover, these disorders often go undiagnosed and poorly treated and only a small proportion is actually presenting to psychiatrist. Higher percentage of mental disorders co exists with physical disorders necessitating the need of linkage between medical and mental health care system.

C-L psychiatry has the potential to help reduce the burden of mental problems in both developed and developing countries from a public health standpoint.

An increased involvement of C-L psychiatrists in the development of primary care services is an important step forward.

Definition

The area of clinical psychiatry that covers clinical, teaching and research activities of psychiatrists and allied mental health professionals in the non-psychiatric divisions of a general hospital.

The designation "Consultation-Liaison suggests two interrelated functions of the consultants as proposed by Lipowski. Expert opinion regarding diagnosis and management of patient's mental and behavioural disorders at the request made by other health professional is considered as consultation. Whereas, the term "Liaison" indicates connecting and linking the groups to serve the objective of effective collaboration. In CL psychiatry, liaison involves interpretation and mediation i.e. consultant psychiatrist not only intercedes between patients and members of treating team but also between mental health and other health professionals respectively.

An effective model of collaborative care with primary care physician can be established by CLpsychiatrist. The active component of such care include effective screening, training and sensitization of staff and regular supervision by a psychiatrist.
There is a growing need for CL psychiatry to become integral and larger part of patient management across all medical settings which require more commitment and time from respective departments.
Presently most of the CL services are restricted to the wards only and their extension to outdoor services would have added benefit of carrying over the established therapeutic alliance for future consultation.
The role of CL psychiatry in tertiary care institute should also involve developing cost effective treatment models, specific non pharmacological intervention thus making patients more adjustable to medical disorders and their treatment compliance in long term.

There are situations when the patients referred in CL psychiatry may not fulfill diagnostic criteria for particular mental disorder, yet they may need support for their psychological issues. It is equally important that CL psychiatry must follow principles of evidence based medicine.

Much emphasis needs to be given to improve C-L psychiatry services and training in India. Escalation of research and training in CL psychiatry as well as involvement of other mental health professionals in process of CL psychiatry may help in this regard. The focus of research should also include assessment of cost effective models in CL psychiatry to help policy makers understand the benefits of CL service and its implementation. 9

The C-L psychiatry as an evolving branch has tremendous scope in dealing with global mental health challenges. Expansion in primary care services and improvement in existing CL services can be achieved by initiatives of consultant psychiatrist who may also guide the new generation psychiatrist by training and teaching and encouraging them to participate in research to develop cost effective modules of CL psychiatry.

History of C.L Psychiatry

CL psychiatry can be considered as a landmark developmental mile stone that has remarkably changed the face of psychiatry practice .With an increasing number of general hospital psychiatric units, mental health issues have been brought much closer to general health care and community. This has resulted in greater acceptance of psychiatric practices in other medical and surgical specialties and ample of opportunities for training and management of physically ill patients with psychiatric co morbidities.

Some of the landmark development in history of CL psychiatry is mentioned in table given below.

Year	Landmark Developments
1818	**Johann Heinroth** Coined term "psychosomatic"
1922	**Felix Deutsch** Proposed the concept of "psychosomatic medicine"
Late 1800s	**Jackson Putnam** Considered being the first consultation psychiatrist.
1902	**JM Mosher** Established the first general hospital psychiatric unit in Albany Hospital
1929	**Henry's** Landmark paper on "Some Modern Aspects of Psychiatry in General Hospital Practice"
1934	**Rockefeller Foundation** Funded for establishment of five psychiatric liaison units in university hospitals
2003	C-L Psychiatry was approved for subspecialty status in psychiatry under the term "Psychosomatic Medicine."

Mental health services in India were restricted to mental hospital set ups until 1930 , when the first general hospital psychiatric unit(GHPUs) was established by Dr Girindra Shekhar of R. G. Kar Medical College and Hospital in Calcutta in 1933 to introduce CL psychiatry as sub specialty. A rapid escalation in number of GHPUs took place in late 1060s and early 1970s.Since then the concept and popularity of GHPU has gained momentum and presently most of the post graduate psychiatry study is takes place in general hospitals, however, the focus on CL psychiatry has not been emphasized much despite this fact. The need of the hour is that CL psychiatry should be given a subspecialty status.

Need for C.L. Psychiatry

Mind and body have close link and bi-directional association is presumed to exist between Psyche and soma, influencing each other. Physical and mental disorders have a lot in common and psychological factors needs to be considered in all disease states. The psychological response of these physical disorders and their management may not reach to a morbid level.

Remarkably emerging evidences suggest biological explanations. Neurochemical, immunological, and endocrine responses to stress are well known. Following points highlights the need of CL psychiatry.

1. Approximately 20% to 46% patients with physical disorders admitted to medical or surgical wards have at least one diagnosable psychological comorbidity. Furthermore, this group has a substantially higher prevalence of psychiatric disorders than the general population.

2. Even subclinical or subthreshold symptoms of a concomitant psychiatric disorder have been linked to unfavourable health outcomes in hospitalised patients, such as longer lengths of stay and excessive use of health care resources.

3. By focusing on comorbid psychiatric symptoms or illnesses, CL psychiatry treatments improve overall health outcomes.

4. In patients with comorbid physical and mental disorders, earlier referral to CL psychiatry is linked to a shorter length of stay.

5. The engagement of CL psychiatry in providing care for patients with medical and psychiatric comorbidity has been linked to a lower rate of readmission after discharge from the hospital over the next few days to months.

6. Early recognition and management of subclinical psychological distress that does not rise to the level of a psychiatric disease has been shown to improve the course and outcome of medically ill patients while also lowering health care expenditures.

7. Interventions provided by the CL psychiatry team have also been linked to enhanced quality of life and other qualitative metrics like subjective experiences for both patients and carers during and after their hospital stay.

8. Imparting teaching and training to other health professionals regarding associated psychological component in CL psychiatry may enhance their acquaintance with the concept and better and cost effective treatment outcome.

Models Of C.L. Psychiatry

Based upon	Approach
Focus of consultation, function & focus of work	Patient oriented
	Crisis Oriented
	Consultee-oriented
	Situation oriented
	Expanded psychiatric consultation

Function	Consultation model
	Liaison model
	Bridge model
	Hybrid model
	Autonomous psychiatric model
Focus of work	Critical care model
	Biological model
	Milieu model
	Integral model

Patient oriented approach - The consultant's primary interest is in the patient. It comprises a psychodynamic appraisal of the patient's personality and reaction to sickness, as well as a diagnostic interview and assessment of the patient.

Crisis oriented approach – Patient's problem and coping methods are quickly assessed and instant remedial interventions provided to address the problem.

Consultee-oriented approach – The focus of this approach is to address the purpose of consultee and his related concern and expectations.
Situation oriented approach- Interpersonal interactions of all the members of the clinical team involved in the care of the patient is the main focus in this approach to understand patient's behavior and the consultee's concern about it.

Expanded psychiatric consultation model- Keeping central focus on patient requiring consultation, this approach includes an operational group that involves the patient, the clinical staff, other patients, and the patient's family.

Consultation model –Patient is the centre of focus..

Liaison model – The consulting physician is the focal point of the liaison model, which includes teaching the physician and the clinical team about the psychological and behavioural components of the patient's problem in addition to providing advice for the patient.

Bridge model- C-L psychiatrist plays a teaching role for the primary care physicians.

Hybrid model- involves psychiatrist as part of multidisciplinary team.

Autonomous psychiatric model- the C-L psychiatrist is not affiliated to any department but is hired by primary care services.

Critical care model- In this model critical care units (ICU,CCU)have CL psychiatrist attached with it who is expected to be involved in patient care and addressing issues of staff.

Biological model- lays emphasis onneuroscience, psychopharmacology and psychological management.

The Milieu model is founded on interpersonal theory and incorporates group components of patient care, staff reaction and interaction, and understanding of ward environment.

Integral model is usually based on an agency, and it entails delivering psychological care as a necessary component of clinical and administrative needs.

Reactive v/s Proactive Consultation Liaison Psychiatry

Reactive CLP refers to the practice of CLP where patient is seen by MHP only after the referral is made from the primary treating team from other specialty. Whereas proactive CLP involves participation of MHP as an active component of Behavioral Intervention Team (BIT) which is a proactive multidisciplinary psychiatric consultation service associated with medical/surgical unit. Proactive model has the advantage of identifying and reducing risk factors interfering with effective care before the problems get entirely manifest.BIT works closely in association with the medical team. It helps through formal and informal consultation, management of behavioral problems, education and training of medical staff, prompt and direct care of complex patients with behavioural problems.BIT also helps in identifying and facilitating transition to proper outpatient or inpatient psychiatric unit. Proactive CLP has several benefits as below:

- Easy access to mental health service
- Reducing length of stay in hospital
- Early detection and treatment
- Education and training of peers regarding management of behavioural problems
- Developing better relationship with other specialty

Categories of patients in C.L. Psychiatry

According to the European Association of CL Psychiatry and the Academy of Psychosomatic Medicine's consensus guidelines, the majority of patients encountered in CL psychiatry practise fall into one of the six groups listed below.:

(1) Individuals with comorbid physical (medical) and psychiatric disorders where the management of each disorder complicates the management of the other. Person with co morbid physical and mental disorders where management of one disorder may complicate the treatment of other
(2) Patients presenting with medically unexplained symptoms presenting as in the clinical services. Patients presenting in clinical service with medically unexplained symptoms
(3) Mental and behavioural disorders attributed to general medical conditions or their management.
(4) Patients with psychiatric disorders presenting to medical setting for diagnostic or therapeutic procedures.
(5) Person presenting with suicidal or self harming behavior in emergency or medical unit.Individuals presenting with suicide or self harming behavior in the medical setting.
(6) Patients with health behavior, personality traits, cognitive function or social condition *that may influence management of medical condition* .

Roles of C.L. Psychiatrist

Liaison psychiatry's expertise is critical in providing complete, integrated care for patients with long-term illnesses and medically unexplained symptoms.
Liaison psychiatry professionals are expected to be experts in the following areas.

- **Ability to develop assessment formulation and treatment plan of complex cases**

Skills to manage complexity in patients care when there is interaction between physical and psychological factors.

- **Active collaboration within health care system**

Explicit knowledge of health care system, enabling them to establish effective liaison with different service systems to ensure appropriate treatment as per requirement of the patients.

- **Management of patients requiring both medical and psychiatric expertise**

  Ability to assess relative contribution of physical and psychological factors in patient's presentation and management including:

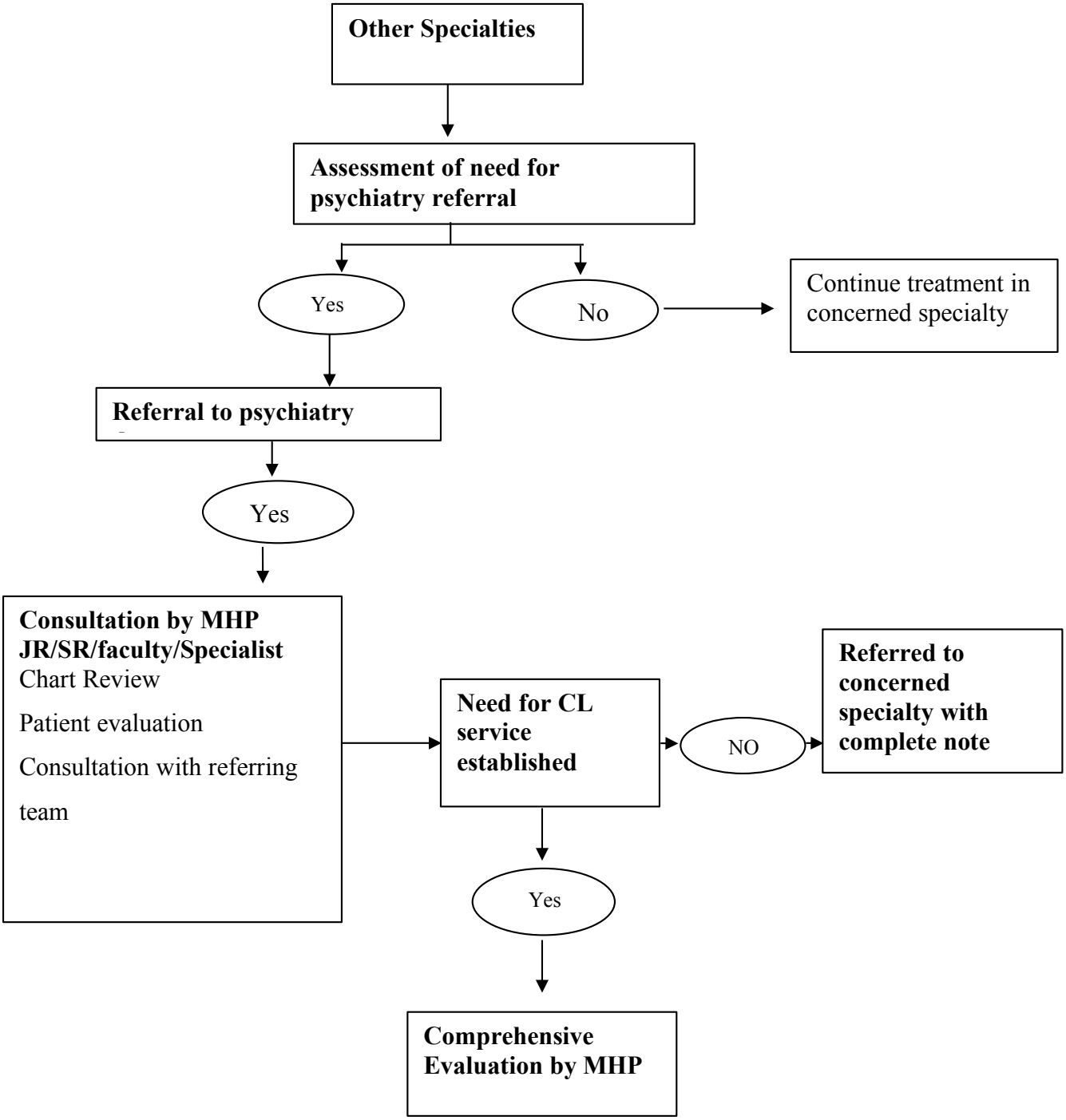
- Adverse effects and potential drug interaction of medications
- Understanding of medical investigations
- Acknowledging patient's concern about his illness.

- **Teaching and Training**

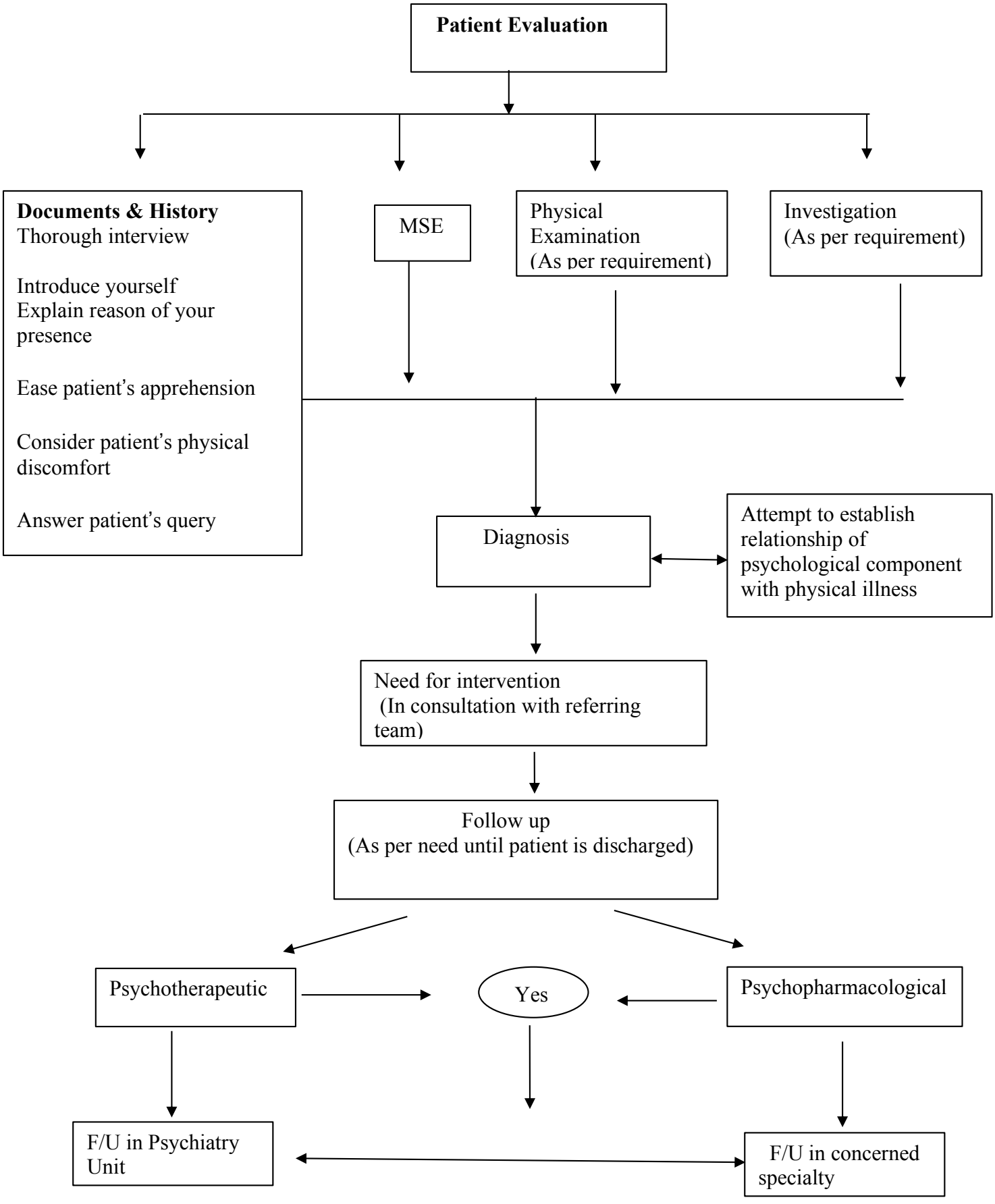
  Teaching and trading are integral part of liaison psychiatry.

- Ad hoc training: on day to day basis during daily clinical work
- Formal training: Scheduled sessions

Steps in CL Psychiatry



Management by MHP



Scope of CL Psychiatry

1. Opportunity to assess patients with psychiatric morbidity and their management in medical/surgical units.
2. Opportunity to delineate the impact of medical illness on origin and presentation of psychiatric disorders and their manifestations and vice versa.
3. Opportunity to formulate a comprehensive biopsychosocial assessment and management plan in consultation with other specialty to provide effective and holistic treatment.
4. Opportunity to assess reaction to physical illness and differentiate the presentation psychiatric illnesses in medical/surgical units.
5. Opportunity to have deep insight in to common pathways of illness and their implications in treatment outcome of the disease.
6. Opportunity to assess and manage physical symptoms with no plausible underlying cause.
7. Opportunity to explore and manage different neuropsychiatric disorders especially delirium.
8. Opportunity to understand particular need of special population with psychiatric co morbidity such as adolescents, old and those with intellectual disabilities and their management.

Role of CL Psychiatry in Medical Practice

Medical practice has largely been benefited by CL psychiatry .Evidently CL psychiatry has significantly highlighted mental and behavioral consequences of medical disorders as well as how psychological issues influence medical illness in terms of origin, course and outcome.
Significant emphasis has been given in consultation licence psychiatry regarding management of psychiatric disorders associated with medical conditions, drug interactions of psychotropic medications with other medicines and psychological symptoms caused by psychotropic medications. There has been a great deal of research in several medical conditions associated with psychiatric symptoms or disorders such as diabetes, heart diseases, cancer,CVA etc.
Role of social psychiatry in emergency setup is widely known and accepted. similarly families and caregivers of the patient with critical condition are helped by CL psychiatrist in dealing with the crisis situation and acceptance of the situation without much stress.
In recent years CL psychiatry has become an integral part of organ transplant team for both donor and recipients .
C L psychiatry has also played significant role in treatment of various psychosomatic disorders in general hospital setup thus reducing cost of treatment. Sympathy towards patient and caregivers as well as effective communication with them by treating team has also been significantly influenced by CL psychiatrist who imparts teaching and training which also focuses on this aspect of soft skills which are very important in day-to-day clinical practice.

Management of patients with physical illness

In 1958, Weissman and Hackett in 1958 suggested sensory deprivation caused by post operative bilateral patching and immobilization, thus making it apparent to ophthalmologists to revise their post operative management strategies.
Kornfeld et al. in 1965, reported Development of delirium following open-heart surgery, appearing after short lucid interval and disappeared shortly after patient left cardiac surgery recovery room . This study affected the architecture of intensive care units (ICUs) and patient management, in addition to the management of heart surgery patients. For example, hospital architects tried to include outside windows, put clocks on the walls, and reorganized nursing operations to allow for more undisturbed sleep.
Friedman and his colleagues investigated the impact of sleep deprivation on intern performance in 1971. Interns used to work every other night and every other weekend at the time. They might work

for 48–72 hours with very less sleep in a major teaching hospital. This essay, which appeared in the New England Journal of Medicine, had a major impact on medical education.
Spiegel et al. reported in the Lancet in 1989 that a year of weekly group therapy for women with metastatic breast cancer reduced distress and increased life expectancy. Later research by Fawzy et al. found a similar impact in melanoma patients.

Robinson et al. looked into stroke prognosis and discovered that depression is linked to a greater fatality rate. Their findings on the usefulness of antidepressants in these patients have been incorporated into the US Public Health Service's therapeutic guidelines for post-stroke rehabilitation.
Interferon, an antiviral drug used to treat hepatitis C, multiple sclerosis, and malignant melanoma, can cause depression and suicidality in up to one-third of patients. Musselman et al., suggested that using paroxetine prophylactically two weeks before therapy greatly lowered the risk of this happening.

In 1970s and 1980s , good understanding about panic attacks and application of this knowledge in the C-L Psychiatry demonstrated significant number of patients with chest pain and normal coronary angiograms as panic disorder. Thus, making panic disorder as an important part of differential diagnosis of cardiac symptoms, thereby reducing frequency of unnecessary investigations and ensuring appropriate treatment.

The Indian Journal of Psychiatry has published a number of different papers.
N. N. Wig (1968) documented examples of post vasectomy syndrome in the general hospital's psychiatric clinic, with the most common pattern being a persistent and disabling neurasthenic hypochondriac state. These elements, however, have not been studied much in Indian psychiatry .
In the IJP, there is some research paperwork from the army set up. Major R. S. Mathur (1977) conducted a survey of 638 troops hospitalised in a military hospital for physical illnesses or trauma, and found that 34.5 percent of them had psychological morbidity, manifesting primarily as sadness and anxiety In the Indian context, a lot of work has been documented in the subject of deliberate self-harm and suicide. R.K. Chadda and S. Shome (1996) discovered that psychiatric consulting services are underutilised by a significant proportion of practitioners.
Cost benefit analysis
Consultation-liaison psychiatry service has the ability to improve quality of care and simultaneously reduces cost of treatment.

Billings et al. reported in 1937 that their psychiatric consulting service at Denver General Hospital reduced patient stays from 28 to 16 days on average.
Levitan and Kornfeld reported positive outcome of a liaison psychiatrist service assigned to an orthopedic service for the patients of fractured femur. With the timely identification and treatment of psychiatric problems, length of stay was significantly shortened with increased chances of returning home .This led to reduction in overall treatment cost.

Smith et al. published their findings in 1986 about educating primary care practitioners of how to apply psychiatric principles to the treatment of hypochondriasis outpatients. These strategies decreased medical costs by 49 percent to 53 percent without affecting patients' health or satisfaction.

Teaching

For consultation-liaison psychiatrists, continuing medical education of medical practitioners has long been a top emphasis. In their article “Psychiatry and Medical Practice in a General Hospital,” published in the New England Journal of Medicine in 1956, Bibring and Kahana classified patients

into personality categories. They avoided psychiatric jargon in favour of language that would help practitioners to recognise these patients in their daily work. They further explained what disease meant to each patient type and how doctors might best handle their predictable behaviours.
Groves published two essays, “Taking Care of the Hateful Patient” and “Management of the Borderline Patient on a Medical or Surgical Ward,” in which he attempted to assist our colleagues in dealing with tough clinical situations by applying our knowledge of psychopathology and psychodynamics. Without a doubt, psychiatry has contributed to the well-being of countless patients by helping physicians develop the skills needed to efficiently and effectively communicate with patients, asking questions that reveal a patient's true concerns, and making an effective psychiatric referral.

End of life care

Muskin, writing in the Journal of the American Medical Association in 1998, pointed out that there are no discussions in the medical literature on the true significance of such a request from any individual patient. If a psychiatrist has a part in right-to-die legislation, it is mainly confined to determining competency. . Muskin emphasised the importance of including the motivation's possible complexity in such a request, as well as the role psychiatric principles can play in determining its genuine meaning.
“Physicians think of death as a defeat and typically react accordingly,” Sherwin Nuland wrote in How We Die. Physician must learn what more can be done,once "doing" is redefined to include comfort in its various forms as a suitable function for a physician. Physicians who are somewhat acquainted with the emotional requirements of physically ill patients, such as consultation-liaison psychiatrists, can take the lead in teaching junior physicians how to effectively deal with dying patients and their families.
Clinical genetics.

The ethical difficulties and psychological ramifications of rapidly developing genetic knowledge are now being confronted by medicine. Clinicians must decide how to effectively deal with new gene markers when they emerge. When and how should this kind of knowledge be applied? What are the consequences of using it? Each genetic test comes with its own set of emotions. As more genetic links are discovered, issues arise, and answers for many specific patients are rarely found in statistical likelihood estimates provided by a genetic counsellor. Psychiatrists that provide consultation-liaison services can assist patients deal with dysphoria and identify the best solutions for them.

C.L. Psychiatry in India
Referral rates for psychiatric services in general hospital are much lower in India (0.15-3.6%) compared to the higher rates(about 10%) of referral in Western countries.A recent on line survey from 90 training centers on practice of CL psychiatry in India reported that CL services are provided as “on-call services.”in three-fourths of the institutes in India.
Only a handful CLP centres include other mental health professionals such as psychiatric nurses, psychiatric social workers, and clinical psychologists. In the majority of CLP teams (60 percent), the junior resident is the initial respondent.Delirium, substance use disorders, self-harm, and depression are the most common diagnostic categories seen in CLP practise across different centers. There is no specific CL psychiatry posting for junior and senior residents at the majority of the centers, and less than half of the centers perform joint academic activities involving various specialties. There are very few research initiatives in which the lead investigator is a psychiatrist.

Equal or more importance was emphasized to be given to CL psychiatry in postgraduate training programs than other subspecialties such as child psychiatry, addiction psychiatry, and geriatric psychiatry by most of the participants .

Psychiatry training is mainly provided in the psychiatry inpatient or psychiatry outpatient setting in most of the centres that provide exposure to psychiatry at the undergraduate level, with only a few institutes giving psychiatry training to undergraduates in the CLP setting.CL services were rated average by most of the participants in their institute. They offered a suggestion to improve CL services by establishing dedicated CL psychaitry team.

Commonly presented Psychiatric patients in C.L. Psychiatry

Diagnosis	Inpatients(%)	Emergency(%)	Outpatients(%)	
Neuroses	28.7-55	51	33.3	
Depression	1.5-24.4	6.2-10.1	15.8-20.0	
Psychotic illness including schizophrenia	3.2-33.3	7.1-13.6	9.3-37.4	
Substance use	1.8-28.9	1.5-35.3	5-14.3	
Psychosomatic, somatoform	0.8-7.7	10.8	3.0-5.0	
Bipolar disorder	2.3-10.4	6	2.0-3.1	
Obsessive compulsive disorder			5.0	
Anxiety	1.1-13.1	3.4-12.3	19.1-38.0	
Dissociation	0.9-8.3	12.8-27.7	2.0	
Delirium	2.8-43.4	4.6-34.1		
Dementia	0.9-3.8	9.5		
Organic Psychosis	0.6-25.5	7	0.8	
Organic disorders			23.2	
Psychosis associated with other physical condition			5.3	
Organic brain syndrome	10.7-19.1			
Organic mental and personality disorder	4.2-4.4	2.6-4.2		
Adjustment reaction	0.4-16.0	1.9-8	1.0	
Post partum psychosis	0.6-2.6			
Psychosexual/ sexual	0.7		3.0	
Personality	0.63-5.3		6.7	

Mental retardation	0.6-7		3.7	
Conduct disorder	0.8			
ADHD	0.4-0.8			
Intentional self harm	2.7-34	5.2-17.0		
Catatonia	0.8			
Munchausen/factitious/malingering	0.2-0.7			
Tic disorder	0.8			
Adverse drug reaction	0.6-2.6			
Other	2.3-12.0		9.0-24	
Nil Psychiatry	1.1-32.1	1.2-12.3	6.5-24.0	

Adapted from Dua D, Grover S. Profile of patients seen in consultation-liaison psychiatry in India: A systematic review. Indian J Psychol Med. 2020;42(6): 503–512

Barriers in effective implementation of C.L Psychiatry

In India CL psychiatry has not been given due recognition as a Sub specialty .More over psychological issues in patients with physical disorders have not been addressed as effectively as desired. Following table summarizes the factors contributing as barrier in effective implementation of CL psychiatry in India.

- Poor representation of psychiatry as a subject in undergraduate medical training.
- Negative attitude for psychiatric disorders by other specialties.
- Inadequate knowledge and lack of skills in doctors from other specialties to identify psychiatric illness and decide when to refer.
- Lack of awareness about their psychological issues in patients and care givers.
- Non acceptance of psychiatric illness by patient and caregivers due to associated stigma.
- Improper diagnosis and inadequate treatment of psychiatric illness by specialist other than psychiatrists.
- Very less referral rate for psychiatric consultation from other specialties.
- Inadequate number of mental health professionals to meet the demand for effective CL psychiatry services.
- Little interest in reference to psychiatry services by treating doctor, considering patients reluctance to seek psychiatric consultation.
- Drop out of patients in CL psychiatry after discharge from the hospital.

Overall associated stigma with mental health disorders is another significant barrier which may give rise to many other situations as mentioned above, thus impeding the referral process.

Strategies to improve CL psychiatry services and future perspective

Considering the large number of patients who need CL services and importance of CL services, still much remains to be developed with regard to CL psychiatry in India. Several

strategies as given below can be adopted to overcome barriers in proliferation of CL psychiatry and its wider implementation.

- Training of mental health professionals in CL psychiatry by institutes with established CL psychiatry units.
- Trainee students should be given ample of opportunity to understand and develop kills in CL psychiatry.
- Exposure of trainee students in emergency and other specialty settings must be ensured to deal with psychological issues in physical disorders.
- Proper structuring of CL psychiatry unit involving participation of psychiatrist, psychologist, psychiatric nurses and doctors from other specialty.
- Prompt and effective response to a referral keeping referring team in loop and regular follow up.
- Proper record keeping of CL services
- Adequate exposure of undergraduates to psychiatric services with special emphasis on CL services
- Expanding the horizon of mental health by discussing different mental health issues at different platforms and not merely restricted to psychiatric illnesses.
- Research in CL psychiatry can provide additional support to vouch for its effectiveness in policy makings.

In large number of patients suffering from psychiatric comorbidity with chronic physical disorders, the management of emotional problems remain neglected. Therefore, if a dent can be made in management of psychiatric comorbidities with chronic physical disorders, it would not only give a due status to the speciality of psychiatry but would also change the quality of life of millions of patients.

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