

## Clinical Practice Guidelines for the management of Depression

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### INTRODUCTION

Depression is a common disorder, which often leads to poor quality of life and impaired role functioning. It is known to be a major contributor to the global burden of diseases and according to World Health Organization (WHO), depression is the fourth leading cause of disability worldwide and it is projected that by 2020, it will be the second most common leading cause of disability. Depression is also associated with high rates of suicidal behaviour and mortality. When depression occurs in the context of medical morbidity, it is associated with increased health care cost, longer duration of hospitalization, poor cooperation in treatment, poor treatment compliance and high rates of morbidity. Depression is also known to be associated with difficulties in role transitions (e.g., low education, high teen child-bearing, marital disruption, unstable employment) and poor role functioning (e.g., low marital quality, low work performance, low earnings). It is also reported to be a risk factor for the onset and persistence of a wide range of secondary disorders. Available data also suggests that between one-third and one-half of patients also experience recurrence of depressive episodes.

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### ASSESSMENT AND EVALUATION (table-1)

Management of depression involves comprehensive assessment and proper establishment of diagnosis. The assessment must be based on detailed history, physical examination and mental state examinations. History must be obtained from all sources, especially the family. The diagnosis must be recorded as per the current diagnostic criteria.

Depression often presents with a combination of symptoms of depressed mood, loss of interest or pleasure, decreased energy and fatigue, reduced concentration and attention, reduced self-esteem and self-confidence, ideas of guilt and unworthiness, bleak and pessimistic views of the future, ideas or acts of self-harm or suicide, disturbed sleep and diminished appetite. Depending on the severity of depression some of these symptoms may be more marked and develop characteristic features that are widely regarded as having special clinical significance. These symptoms are known as somatic symptoms of depression and include symptoms of loss of interest or pleasure in activities that are normally enjoyable, lack of emotional reactivity to normally pleasurable surroundings and events, waking up in the morning 2 hours or more before the usual time, depression worse in the morning, objective evidence of definite psychomotor retardation or agitation (remarked on or reported by other people), marked loss of appetite, weight loss (often defined as 5% or more of body weight in the past month) and marked loss of libido. It is important to note that for the diagnosis of depressive disorder these symptoms need to be present for at least 2 weeks and need to be associated with psychosocial dysfunction.

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**Table 1: Components of assessment and evaluation**

**Basic assessments**

- Complete history with information from all possible sources
- Physical examination- look for thyroid swelling, evidence for malnutrition or any specific nutritional deficiency
- Record blood pressure, weight and wherever indicated body mass index and waist circumference
- Mental state examination
- Establish diagnosis according to current diagnostic criteria
- Differential diagnosis by ruling out secondary depression
- Rule out bipolar disorder, premenstrual dysphoric disorder
- Assess the severity, specifier, subtype of depression
- Areas to be evaluated: symptom-severity, symptom-dimensions (psychotic symptoms, catatonic symptoms, melancholic symptoms, reverse vegetative symptoms and cognitive symptoms), comorbid physical, psychiatric and substance use conditions, risk of harm to self and others, level of functioning and socio-cultural milieu of the patient
- Basic investigations: haemogram, blood sugars and lipid levels, liver functions, renal functions, thyroid function test (if indicated)
- Assessments of caregivers: knowledge and understanding of the illness, attitudes and beliefs regarding treatment, impact of the illness on them, personal and social resources
- Ongoing assessments: response to treatment, side effects, treatment adherence, the impact of patient's immediate environment, disability assessments, other health-care needs, ease of access and relationship with the treatment team

**Additional/Optional assessments**

- Use of standardized rating scales to rate all aspects of the illness
- Neuroimaging especially in those with first-episode of depression seen in late or very late age; those have neurological signs, those having treatment resistant depression

**Table 2: Some of the physical illnesses commonly associated with depression**

- Epilepsy
- Post stroke
- Parkinson's Disease
- Multiple Sclerosis
- Degenerative Brain Disease
- Alzheimer's Disease
- Coronary Artery
- Disease
- Depression in Malignancy
- Hypothyroidism
- Hyperthyroidism
- Hyperparathyroidism
- Cushing's Syndrome
- Addison's disease
- Diabetes mellitus

Some of the patients with depression may present with predominant complaints of aches, pains and fatigue and they may not report sadness of mood on their own. A careful evaluation of these patients often reveals the underlying features of depression. However, it is important to note that many patients with depression will also have associated anxiety symptoms. With increasing severity of depression patients may report psychotic symptoms and may also present with catatonic features. Thorough assessment also ought to focus on evaluation for comorbid substance abuse/dependence. Careful history of substance intake need to be taken to evaluate the relationship of depression with substance intoxication, withdrawal and abstinence. Whenever required appropriate tests like, urine or blood screens (with prior consent) may be used to confirm the existence of comorbid substance abuse/dependence.

Many physical illnesses are known to have high rates of depression. In some situations the physical illnesses have causative role in development of depression, whereas in other situations the relationship/co-occurrence is due to common etiology. Some of the physical illnesses commonly associated with depression are listed in Table-2. When depression occurs in relation to physical illness attempt may be made to clearly delineate the symptoms of depression and physical illness. Further, while making the diagnosis, it maybe clearly mentioned as to which diagnostic approach [i.e., inclusive approach (*symptoms are counted whether or not they might be attributable to physical illness*), substitute approach (*nonsomatic symptoms are substituted with somatic symptoms*), exclusive approach (*somatic symptoms are deleted from the diagnostic criteria*) or best estimate approach] was followed. Further, while reviewing the treatment history of medical illnesses, medication induced depression **must** be kept in mind, as many medications are known to cause depression (Table-3).

It is always important to take the longitudinal life course perspective into account to evaluate for previous episodes and presence of symptoms of depression amounting to

**Table 3: Medications known to cause depression**

<b>Cardiovascular drugs</b>	Azathioprine	Ampicillin	Penicillin G	Benzodiazepines	Efavirenz
ACE inhibitors	Bleomycin	Chloramphenicol	procaine	Chloral hydrate	Enfuvirtide
Calcium channel blockers	Cisplatin	Methylphenidate (Ritalin)	Streptomycin	Ethanol	Saquinavir
Clonidine	Cyclophosphamide	Chloroquine	Sulfonamides	<b>Other drugs</b>	Zidovudine
Digitalis	Doxorubicin	Clofazimine	Tetracycline	Choline	<b>Anticonvulsants</b>
Guanethidine	Vinblastine	Cycloserine	Trimethoprim	Cimetidine	Ethosuximide
Hydralazine	Vincristine	Cyclosporine	<b>Hormones</b>	Disulfiram	Phenobarbital
Methyldopa	<b>Antiparkinsonian drugs</b>	Dapson	Adrenocorticotropin	Lecithin	Phenytoin
Procainamide	Amantadine	Ethambutol	Anabolic steroids	Methylesergide	Primidone
Propranolol	Bromocriptine	Ethionamide	Glucocorticoids	Phenylephrine	Tiagabine
Reserpine	Levodopa	Foscarnet	Oral contraceptives	Physostigmine	Vigabatrin
Thiazide diuretics	<b>Stimulants</b>	Ganciclovir	<b>Antipsychotic drugs</b>	Ranitidine	<b>Anti-inflammatory agents</b>
Guanabenz	Amphetamines	Griseofulvin	Fluphenazine	Statins	NSAIDS
Zolamide diuretics	(withdrawal)	Isoniazid	Haloperidol	Tamoxifen	
<b>Chemotherapeutics</b>	Caffeine	Metoclopramide	<b>Sedatives and antianxiety drugs</b>	<b>Antiretroviral drugs</b>	
6-Azaauridine	Cocaine (withdrawal)	Metronidazole		Atazanavir	
Asparaginase	<b>Anti-infective agents</b>	Nalidixic acid	Barbiturates		
		Nitrofurantoin			

dysthymia. Evaluation of history also takes into consideration the relationship of onset of depression with change in season (seasonal affective disorder), peripartum period and phase of menstrual cycle. Further, the longitudinal course approach may also take into account response to previous treatment and whether the patient achieved full remission, partial remission and did not respond to treatment.

An important aspect of diagnosis of depression is to rule out bipolar disorder. Many patients with bipolar disorder present to the clinicians during the depressive phase of illness and spontaneously do not report about previous hypomanic or manic episodes. Careful history from the patient and other sources (family members) often provide important clues for the bipolar disorder. It is often useful to use standardized scales like mood disorder questionnaire to rule out bipolarity. Treating a patient of bipolar depression as unipolar disorder can increase the risk of antidepressant

induced switch. Presence of psychotic features, marked psychomotor retardation, reverse neurovegetative symptoms (excessive sleep and appetite), irritability of mood, anger, family history of bipolar disorder and early age of onset need to alert the clinicians to evaluate for the possibility of bipolar disorder, before concluding that they are dealing with unipolar depression.

Area to be covered in assessment include symptom dimensions, symptom-severity, comorbid psychiatric and medical conditions, particularly comorbid substance abuse, the risk of harm to self or others, level of functioning and the socio-cultural milieu of the patient.

In case patient has received treatment in the past, it is important to evaluate the information in the form of type of antidepressant used, dose of medication used, compliance with medication, reasons for poor compliance, reasons for

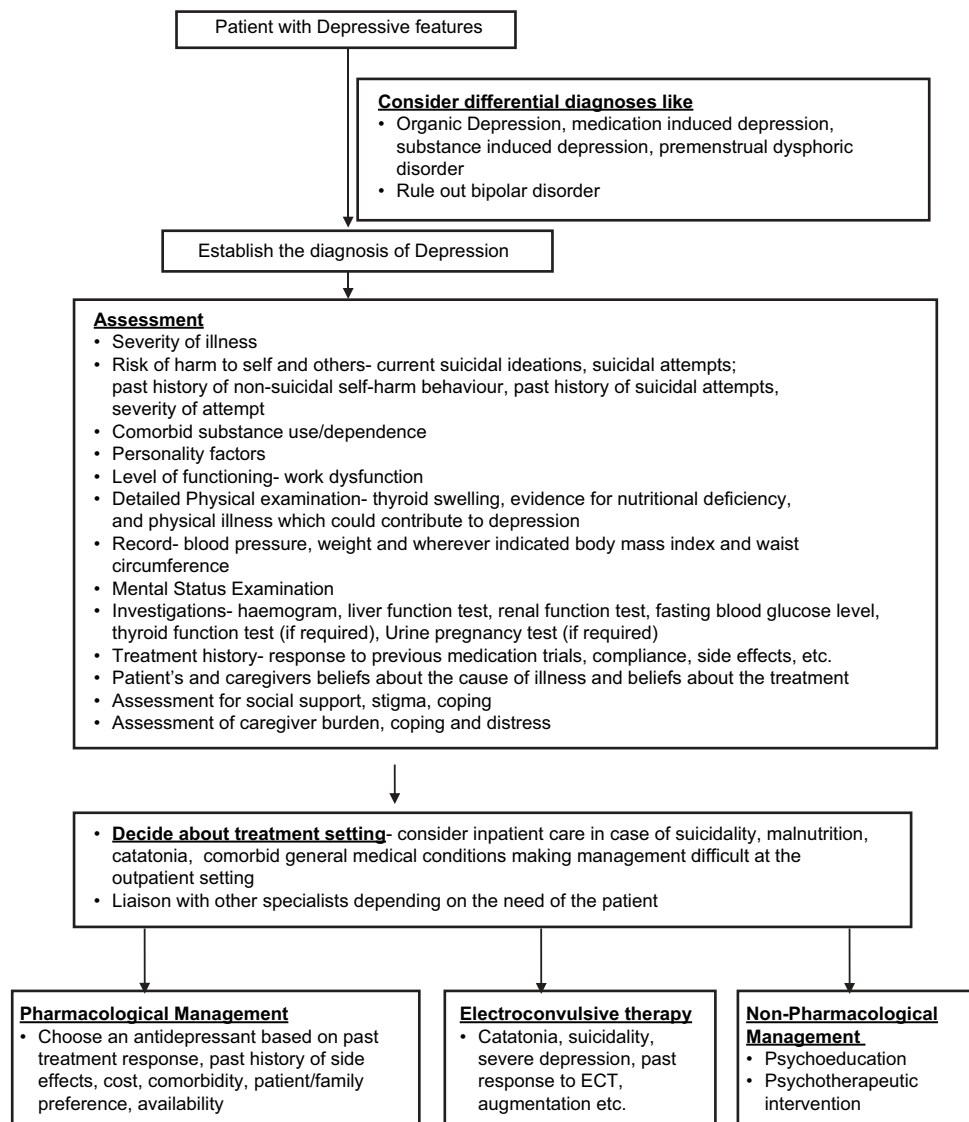


Figure 1: Initial evaluation and management plan for Depression

discontinuation of medication, response to treatment, side effects experienced etc. If the medications were changed, then the reason for change is also to be evaluated.

Wherever possible, unstructured assessments need to be supplemented by ratings on appropriate standardized rating scales. Depending on the need, investigations need to be carried out. The use of neuroimaging may be indicated in those with first-episode of depression seen in late or very late age; those have neurological signs, those having treatment resistant depression.

Besides, patients, information about the illness need to be obtained from the caregivers too and their knowledge and understanding of the illness, their attitudes and beliefs regarding treatment, the impact of the illness on them and their personal and social resources need to be evaluated.

### FORMULATING A TREATMENT PLAN (FIGURE-1)

Formulation of treatment plan involves deciding about treatment setting, medications and psychological treatments to be used. Patients and caregivers may be actively consulted while preparing the treatment plan. A practical, feasible and flexible treatment plan can be formulated to address the needs of the patients and caregivers. Further the treatment plan can be continuously re-evaluated and modified as required.

### EVALUATE THE SAFETY OF PATIENT AND OTHERS

A careful assessment of the patient's risk for suicide should be done. During history inquiry for the presence of suicidal ideation and other associated factors like presence of psychotic symptoms, severe anxiety, panic attacks and alcohol or substance abuse which increases the risk of suicide need to be evaluated. It has been found that severity of depressive symptomatology is a strong predictor of suicidal ideation over time in elderly patients. Evaluation also includes history of past suicide attempts including the nature of those attempts. Patients also need to be asked about suicide in their family history. During the mental status examinations besides enquiring about the suicidal ideations, it is also important to enquire about the degree to which the patient intends to act on the suicidal ideation and the extent to which the patient has made plans or begun to prepare for suicide. The availability of means for suicide be inquired about and a judgment may be made concerning the lethality of those means. Patients who are found to possess suicidal or homicidal ideation, intention or plans require close monitoring. Measures such as hospitalization may be considered for those at significant risk.

### CHOICE OF TREATMENT SETTINGS

Majority of the cases of depression seen in the clinical setting are of mild to moderate severity and can be managed

at the outpatient setting. However, some patients have severe depression which may be further associated with psychotic symptoms, catatonic symptoms, poor physical health status, suicidal or homicidal behaviour etc. In such cases, careful evaluation is to be done to decide about the treatment setting and whenever necessary inpatient care may be offered. In general, the rule of thumb is that the patients may be treated in the setting that is most safe and effective. Severely ill patients who lack adequate social support outside of a hospital setting may be considered for admission to a hospital whenever feasible. The optimal treatment setting and the patient's ability to benefit from a different level of care may be re-evaluated on an ongoing basis throughout the course of treatment. Some of the common indications for inpatient care are shown in Table-4.

**Table 4: Some indications for inpatient care during acute episodes**

- Presence of suicidal behaviour which puts the life of the patient at risk
- Refusal to eat which puts the life of patient at risk
- Severe malnutrition
- Catatonia
- Presence of general medical or comorbid psychiatric conditions that make outpatient treatment unsafe or ineffective

All inpatients should have accompanying family caregivers. In case inpatient care facilities are not available, than the patient and/or family need to be informed about such a need and admission in nearest available inpatient facility can be facilitated.

### THERAPEUTIC ALLIANCE

Irrespective of the treatment modalities selected for patients, it is important for the psychiatrist to establish a therapeutic alliance with the patient. A strong treatment alliance between patient and psychiatrist is crucial for poorly motivated, pessimistic depressed patient who are sensitive to side effect of medications. A positive therapeutic alliance always generates hope for good outcome.

### ENHANCED TREATMENT COMPLIANCE

The successful treatment of major depressive disorder requires adequate compliance to treatment plan. Patients with depressive disorder may be poorly motivated and unduly pessimistic over their chances of recovery with treatment. In addition, the side effect or requirements of treatment may lead to non-adherence. Patients are to be encouraged to articulate any concern regarding adherence and clinicians need to emphasize the importance of adherence for successful treatment. Simple measures which can help in improving the compliance are given in table-5.

## ADDRESS EARLY SIGNS OF RELAPSE

Many patients with depression experience relapse. Accordingly, patients as well as their families if appropriate may

be educated about the risk of relapse. They can be educated to identify early signs and symptoms of new episodes. Patients can also be asked to seek adequate treatment as early in the course of a new episode as possible to decrease the likelihood of a full-blown relapse or complication.

**Table 5: Measures which can improve medication compliance**

- When and how often to take medicines
- Preferably give once a day dosing
- Prescribe minimum number of tablets
- Always ask the patient about kind of formulation (e.g. tablet, capsule etc) which they would prefer to take
- Check the whole prescription to avoid duplication of medication
- Explain the patient that the beneficial effect will be seen only after 2-4 weeks of intake of medications
- Explain the patient the need to take medication even after feeling better
- Explanation of side effects, If patients asks about the side effects- explain the patient about the same
- Explain the patient as to what to do- if they encounter side effects
- Encourage the patient to report side effects
- The need to consult with psychiatrist before discontinuing medications

## TREATMENT OPTIONS FOR MANAGEMENT FOR DEPRESSION

Treatment options for management of depression can be broadly be divided into antidepressants, electroconvulsive therapy (ECT) and psychosocial interventions. Other less commonly used treatment or treatments used in patients with treatment resistant depression include repetitive transcranial magnetic stimulation (rTMS), light therapy, transcranial direct stimulation, vagal nerve stimulation, deep brain stimulation and sleep deprivation treatment. In many cases benzodiazepines are used as adjunctive treatment, especially during the initial phase of treatment.

**Table 6: Antidepressants Armamentarium**

Antidepressant	Usual dose range (mg/day)	Common side effects
<b>Selective serotonin reuptake inhibitors (SSRI)</b>		
Fluoxetine	20-80	Sexual dysfunction, GI distress, weight loss/gain, anxiety, insomnia
Paroxetine	20-60	
Fluvoxamine	50-300	
Sertraline	50-200	
Citalopram	20-40	
Escitalopram	10-20	
<b>Tricyclic tertiary amines (TCAs)</b>		
Amitriptyline	50-200	Sexual dysfunction, anticholinergic effects, drowsiness, orthostasis, conduction abnormalities, mild GI distress, weight gain
Doxepin	75-300	
Imipramine	75-300	
Clomipramine	75-300	
<b>Tricyclic Secondary Amines</b>		
Desipramine	100-300	Mild GI distress, high risk of seizure after 450 mg/day
Nortriptyline	25-150	
Protriptyline	15-20	
<b>Tetracyclic</b>		
Maprotiline	50-75	
<b>Unicyclic</b>		
Bupropion	150-450	
<b>Norepinephrine Serotonin reuptake Inhibitors (NSRI)</b>		
Venlafaxine	75-300	Mild anticholinergics effects, drowsiness, conduction abnormalities, GI distress
Duloxetine	20-60	
Milnacipran	50-200	
Desvenlafaxine		
<b>Norepinephrine Serotonin Reuptake Enhance (NSRE)</b>		
Tianeptine	25-50	Nausea, constipation, abdominal pain, headache, dizziness and changes in dreaming
<b>Noradrenaline and Specific Serotonin Antidepressants (NaSSA)</b>		
Mirtazapine	15-45	Mild anticholinergic effects, drowsiness, orthostasis, conduction abnormalities, GI distress, weight gain
<b>Atypical antidepressants/Serotonin Modulators</b>		
Trazadone	150-300	Mild anticholinergic effects, drowsiness, orthostasis, conduction abnormalities, GI distress, weight gain, severe hepatotoxicity
Nefazodone	100-300	

*Contd...*

**Table 6: Contd...**

Antidepressant	Usual dose range (mg/day)	Common side effects
<b>Reversible Selective Mono Amine Oxidase Inhibitors (RIMA)</b>		
<b>Moclobemide</b>		
<b>Mono Amine Oxidase Inhibitors (MAOI)</b>		
Phenelzine	45-90	Orthostatic hypotension, drowsiness, insomnia, headaches
Isocarboxazid	30-60	
Tranylcypromine	20-60	
<b>Serotonin partial agonist reuptake inhibitor (SPARI)</b>		
Vilazodone	20-40	Diarrhea, nausea or vomiting, and insomnia

**Table 7: Factors that determine the selection of Antidepressant Drug****Patient specific**

- Patients preference
- Previous history of response/tolerability to medication in the patient or family member
- Past side effects with medication
- Other medication being taken – drug interactions
- Patient's age – with increasing age the pharmacokinetic and pharmacodynamic changes become more important
- Comorbid medical illness (e.g., glaucoma, cardiac conditions)
- Comorbid psychiatric disorder/symptoms
- Gender issues – sexual dysfunction
- Intellectual and psychological capacities

**Drug specific**

- Side effects
- Cost
- Dosing strategy
- Type of formulation - Tablet, Cap, Syrup
- Safety in overdose (Relative Toxicity) - fatal overdose is significantly
- Lower with SSRIs than with tricyclic antidepressants

Additionally in some cases, lithium and thyroid supplements may be used as an augmenting agent when patient is not responding to antidepressants.

**Antidepressants**

Large numbers of antidepressants (Table-6) are available for management of depression and in general all the antidepressants have been shown to have nearly equal efficacy in the management of depression. Antidepressant medication may be used as initial treatment modality for patients with mild, moderate, or severe depressive episode. The selection of antidepressant medications may be based on patient specific and drug specific factors, as given in Table-7. In general, because of the side effect and safety profile, selective serotonin reuptake inhibitors (SSRIs) are considered to be the first line antidepressants. Other preferred options include tricyclic antidepressants, mirtazapine, bupropion, and venlafaxine. Usually the medication must be started in the lower doses and the doses must be titrated, depending on the response and the side effects experienced.

**Dose and duration of antidepressants**

Patients who have started taking an antidepressant medication should be carefully monitored to assess the

response to pharmacotherapy as well as the emergence of side effects and safety. Factors to consider when determining the frequency of monitoring include severity of illness, patient's co-operation with treatment, the availability of social support and the presence of comorbid general medical problems. Visits may be kept frequent enough to monitor and address suicidality and to promote treatment adherence. Improvement with pharmacotherapy can be observed after 4-6 weeks of treatment. If at least a moderate improvement is not observed in this time period, reappraisal and adjustment of the pharmacotherapy should be considered.

**Psychotherapeutic interventions**

A specific, effective psychotherapy may be considered as an initial treatment modality for patients with mild to moderate depressive disorder. Clinical features that may suggest the use of a specific psychotherapy include the presence of significant psychosocial stressors, intrapsychic conflict and interpersonal difficulties. Patient's preference for psychotherapeutic approaches is an important factor that may be considered in the decision to use psychotherapy as the initial treatment modality. Pregnancy, lactation, or the wish to become pregnant may also be an indication for psychotherapy as an initial treatment. Various psychotherapeutic interventions which may be considered based on feasibility, expertise available and affordability are shown in Table-8.

Cognitive behavioral therapy (CBT) and interpersonal therapy are the psychotherapeutic approaches that have the best documented efficacy in the literature for management of depression. When psychodynamic psychotherapy is used as specific treatment, in addition to symptom relief it is frequently with broader long term goals.

The psychiatrist should take into account multiple factors when determining the frequency of sessions for individual patients, including the specific type and goals of psychotherapy, the frequency necessary to create and maintain a therapeutic relationship, the frequency of visits required to ensure treatment adherence, and the frequency necessary to monitor and address suicidality. The frequency

of outpatient visits during the acute phase generally varies from once a week in routine cases to as often as several times a week. Regardless of the type of psychotherapy selected, the patient's response to treatment should be carefully monitored. For a given patient, time spent and frequency of visit may be decided by the psychiatrist.

#### Psychoeducation to the patient and, when appropriate, to the family

Education concerning depression and its treatments can be provided to all patients. When appropriate, education can also be provided to involved family members. Specific educational elements may be helpful in some circumstances, e.g. that depression is a real illness and that effective treatments are both necessary and available may be crucial for patients who attribute their illness to a moral defect or witch craft. Education regarding available treatment options will help patients make informed decisions, anticipate side effects and adhere to treatments. Another important aspect of providing education is informing the patient and especially family about the lag period of onset of action of antidepressants. Important components of psychoeducation are given in Table-9.

#### Combination of pharmacotherapy and Psychotherapy

There is class of patients who may require the combination of pharmacotherapy and psychotherapy. In general, the same issues that influence the choice of medication or psychotherapy when used alone should be considered when choosing treatments for patients receiving combined therapy.

### PHASES OF ILLNESS/TREATMENT

Management of depression can be broadly divided into three phases, i.e., acute phase, continuation phase and maintenance phase. Maintenance phase of treatment is usually considered when patient has recurrent depressive disorder.

### ACUTE PHASE TREATMENT

The goal of acute phase treatment is to achieve remission, as presence of residual symptoms increase the risk of chronic depression, poor quality of life and also impairs recovery from physical illness. Treatment generally results in improvement in quality of life and better functional capacity. The various components of acute phase treatment are shown in Table-10 and the treatment algorithm is shown in figure-2 and 3.

In acute phase psychiatrist may choose between several initial treatment modalities, including pharmacotherapy, psychotherapy, the combination of medication and psychotherapy, or ECT. Selection of an initial treatment modality is usually influenced by both clinical (e.g. severity of symptoms) and other factors (e.g. patient preference).

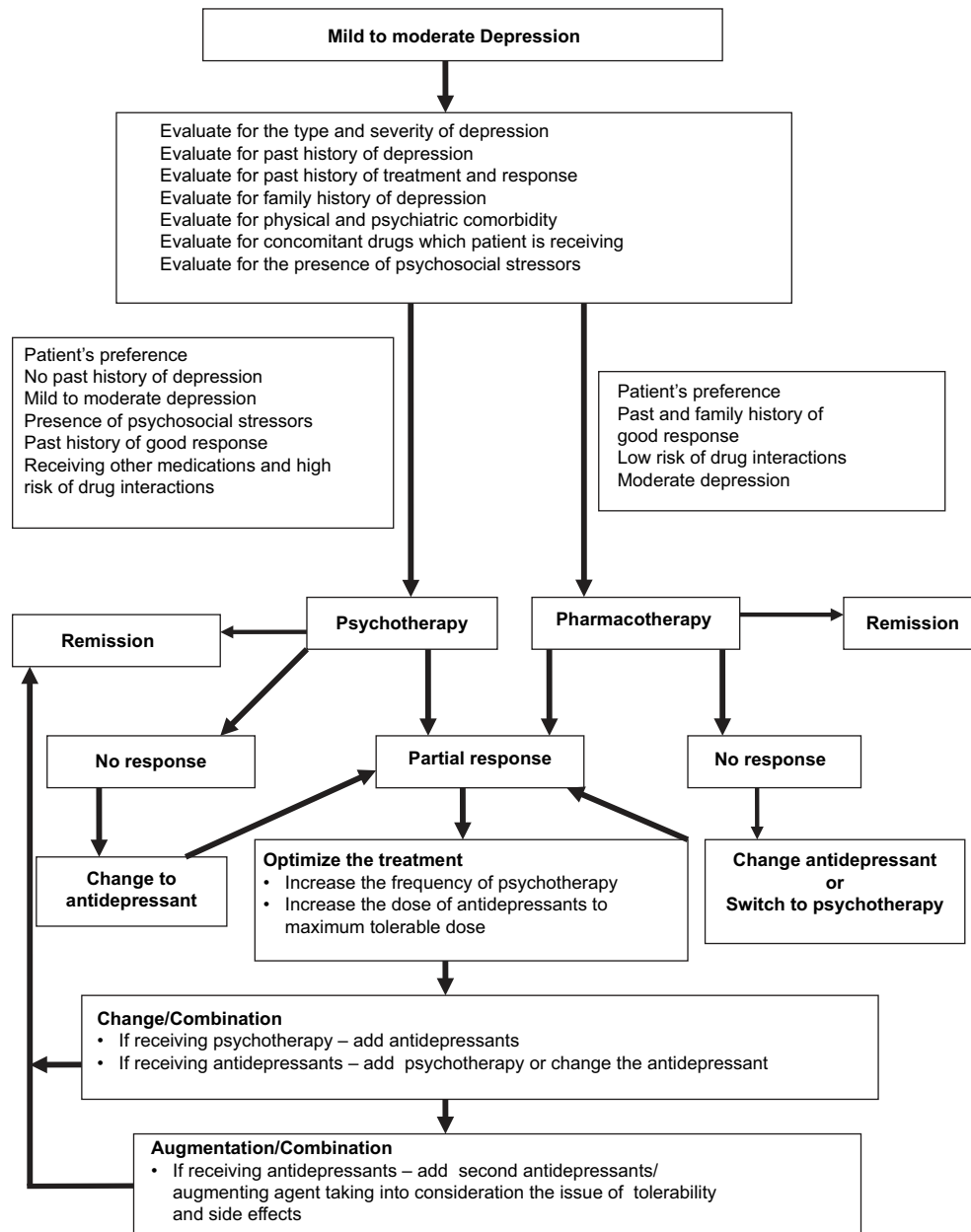
Antidepressant medication may be used as initial treatment modality for patients with mild, moderate, or severe major depressive disorder. Clinical features that may suggest that medication are the preferred treatment modality includes history of prior positive response to antidepressant medication, severity of symptoms, significant sleep and appetite disturbance, 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 initial selection of an antidepressant medication is largely be based on the anticipated side effects, the safety or tolerability of these side effects for individual patients, patient preference and comorbid physical illnesses.

**Dose and duration of antidepressants:** Once an antidepressant medication has been selected, it can be started initially at lower doses and careful monitoring to

**Table 8: Psychotherapeutic interventions for Depression**

Type of therapy	
<b>Cognitive Behaviour Therapy (CBT)</b>	<ul style="list-style-type: none"> <li>Identifying problems, Identifying cognitive distortions/errors, generating alternative thoughts, problem solving, mastery and pleasure rating, activity scheduling, anxiety management strategies- relaxation exercises</li> </ul>
<b>Interpersonal Therapy (IPT)</b>	<ul style="list-style-type: none"> <li>Focuses on losses, role disputes and transitions, social isolation, deficits in social skills, and other interpersonal factor that may impact on the development of depression</li> </ul>
<b>Supportive psychotherapy</b>	<ul style="list-style-type: none"> <li>Allowing the patient to ventilate, providing emotional support, guidance, increasing the patient's self-esteem, accepting feelings at face value, enhancing hope, enhancing adaptive coping</li> </ul>
<b>Behavioral Therapy (BT)</b>	<ul style="list-style-type: none"> <li>Activity scheduling, social skills training and problem solving</li> </ul>
<b>Marital Therapy (MT)</b>	<ul style="list-style-type: none"> <li>Marital therapy conceptualizes depression as an interpersonal context such that both members of the marital dyad are included in therapy. Treatment includes behavioral exchange, communication training, problem solving, and resolution of conflict around issues such as financial, sex, affection, parenting, and intimacy</li> </ul>
<b>Family Therapy</b>	<ul style="list-style-type: none"> <li>When interpersonal problems in the context of pathological family dynamics are responsible for depression, than family therapy may be considered. It would involve all the family members and include similar principles as for marital therapy</li> </ul>
<b>Brief Psychodynamic Psychotherapy (BPD)</b>	<ul style="list-style-type: none"> <li>The premise of brief psychodynamic psychotherapy is that depressive symptoms remit as patient learns new methods to cope with inner conflicts. Several different approaches have been described</li> </ul>



**Figure -2:** Treatment algorithm of mild to moderate Depression

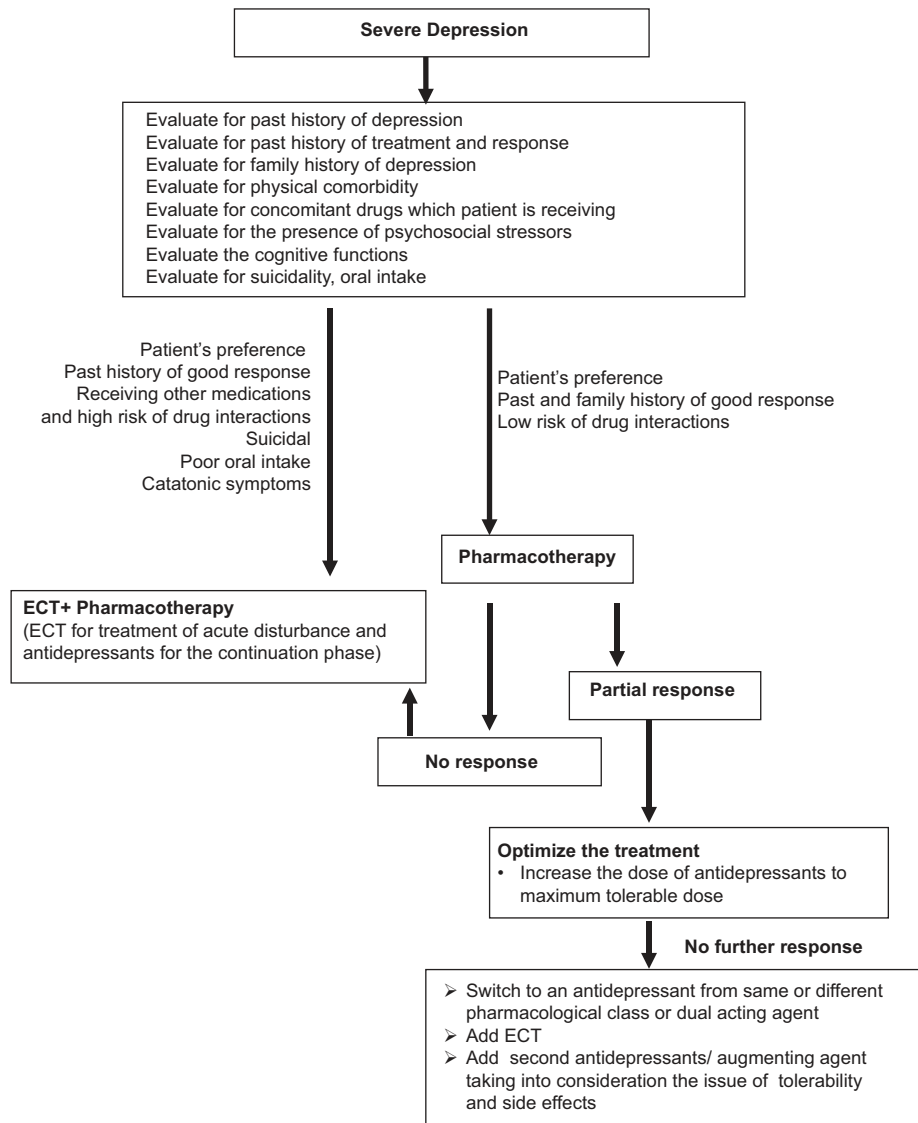
**Table 9: Basic components of Psychoeducation**

- Assessing the knowledge of the patient and caregivers about aetiology, treatment and prognosis
- Explain about the diagnosis and symptoms of depression
- Explain that depression is a medical disorder which is treatable
- Explain about the lag period of onset of action
- Provide information about aetiology
- Provide information about treatment in terms of available options, their efficacy/effectiveness, side effects, duration of use
- Discuss about importance of medication and treatment compliance
- Provide information about possible course and long term outcome
- Discuss about problems of substance abuse, interpersonal conflict, stress etc
- Discuss about how to deal with day today stress
- Discuss about communication patterns, problem solving etc
- Enhancing adaptive coping to deal with persistent/residual symptoms
- Discuss about relapse and how to identify the early signs of relapse
- Encourage healthy life styles

be done to assess the response to pharmacotherapy as well as the emergence of side effects, clinical conditions, and safety. Factors to consider when determining the frequency of monitoring include severity of illness, patient's cooperation and presence with treatment, and availability of social support and presence of comorbid general medical problems. Visits may be frequent enough to monitor and address suicidality and to promote treatment adherence. Improvement with pharmacotherapy can be observed after 4-6 weeks of treatment. If at least a moderate improvement is not observed in this time period, reappraisal and adjustment of the pharmacotherapy maybe considered.

In the initial phase, depending on the symptom severity and type of symptoms, such as presence of insomnia or anxiety,





**Figure 3: Treatment algorithm of Severe Depression**

**Table 10: Management in the acute phase**

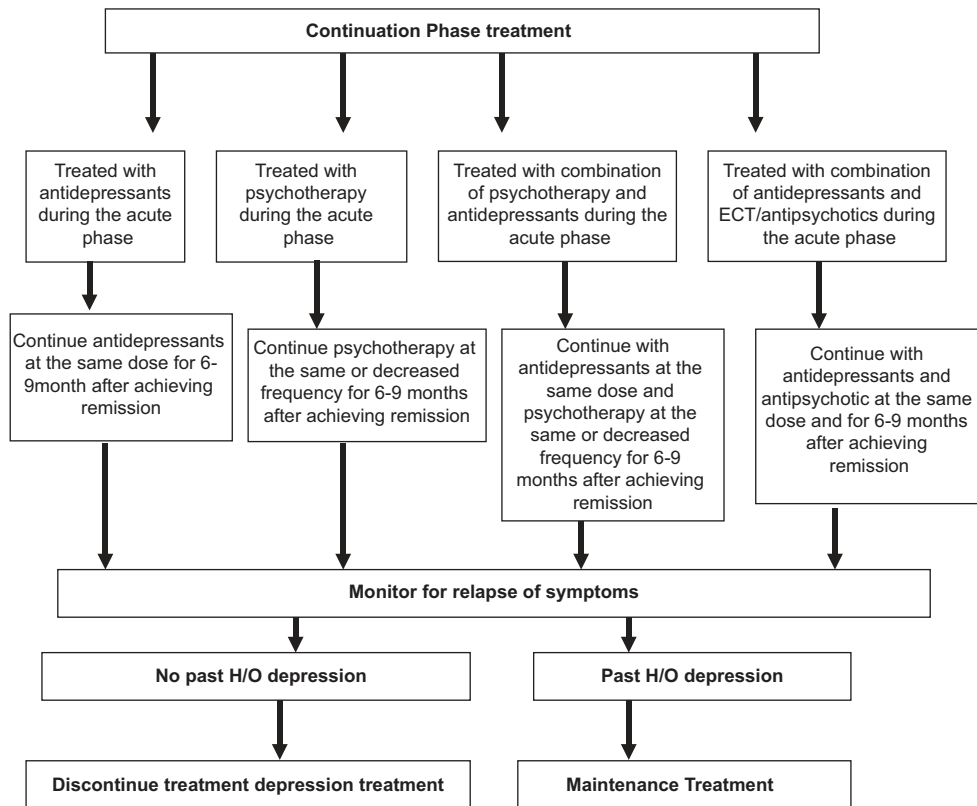
- Comprehensive assessment (psychiatric/medical/psychosocial)
- Deciding on goals of treatment
  - Achieving remission
  - Ensure safety of patient and others
- Choice of treatment setting
- Choosing a treatment modality: antidepressant medication, psychotherapy, combined treatment with antidepressant and psychotherapy
- Use of adjunctive medications when indicated
- Use of ECT when indicated
- Psychoeducation

benzodiazepines or other hypnotics may be used for short duration.

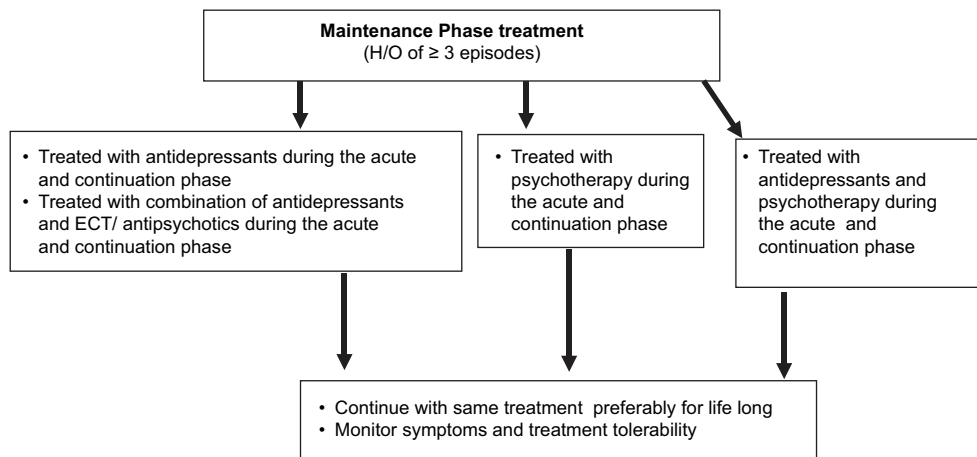
**Failure to response:** If at least some improvement (>25%) is not observed following 4 week of pharmacotherapy, a reappraisal of the treatment regimen be conducted and a change in antidepressant may be considered. When

patient shows 25-50% improvement during the initial 4 weeks of antidepressant trial, the dose must be optimized to the maximum tolerable dose. If there is less than 50% improvement with 6-8 weeks of maximum tolerable dose and the medication compliance is good, a change in antidepressant may be considered.

If after 4-8 weeks of treatment, if a moderate improvement is not observed, then a thorough review and reappraisal of the diagnosis, complicating conditions and issues, and treatment plan may be conducted. Reappraisal of the treatment regimen may also include evaluation of patient adherence and pharmacokinetic/pharmacodynamic factors. Following this review, the treatment plan can be revised by implementing one of several therapeutic options, including maximizing the initial medication treatment, switching to another antidepressant medication, augmenting antidepressant medications with other agents/psychotherapy/ECT. Maximizing the initial



**Figure 4:** Treatment algorithm for continuation phase treatment of depression



**Figure 5:** Treatment algorithm for maintenance phase of depression

treatment regimen is perhaps the most conservative strategy. While using the higher therapeutic doses, patients are to be closely monitored for an increase in the severity of side effects or emergence of newer side effects.

Switching to a different antidepressant medication is a common strategy for treatment-refractory patients, especially those who have not shown at least partial response to the initial medication regimen. There is no consensus about switching and patients can be switched to an antidepressant medication from the same pharmacologic class (e.g., from an

SSRI to another SSRI) or to one from a different pharmacologic class (e.g., from an SSRI to a tricyclic antidepressant). Some expert suggests that while switching, a drug with a different or broader mechanism of action may be chosen.

Augmentation of antidepressant medications may be helpful, particularly for patients who have had a partial response to initial antidepressant monotherapy. Options include adding a second antidepressant medication from a different pharmacologic class, or adding another adjunctive medication such as lithium, psychostimulants, modafinil, thyroid hormone,

an anticonvulsant etc. Adding, changing, or increasing the intensity of psychotherapy may be considered for patients who do not respond to medication treatment. Following any change in treatment, close monitoring need to be done. If at least a moderate level of improvement in depressive symptoms is not seen after an additional 4–8 weeks of treatment, another thorough review need to be done. This reappraisal may include verifying the patient's diagnosis and adherence; identifying and addressing clinical factors that may be preventing improvement, such as the presence of comorbid general medical conditions or psychiatric conditions (e.g., alcohol or substance abuse); and identifying and addressing psychosocial issues that may be impeding recovery. If no new information is uncovered to explain the patient's lack of adequate response, depending on the severity of depression, ECT maybe considered.

**Choice of a specific psychotherapy:** Out of the various psychotherapeutic interventions used for management of depression, there is robust level of evidence for use of CBT. The major determinants of type of psychotherapy are patient preference and the availability of clinicians with appropriate training and expertise in specific psychotherapeutic approaches. Other clinical factors which will influence the type of psychotherapy include the severity of the depression. Psychotherapy is usually recommended for patients with depression who are experiencing stressful life events, interpersonal conflicts, family conflicts, poor social support and comorbid personality issues.

The optimal frequency of psychotherapy may be based on specific type and goals of the psychotherapy, the frequency necessary to create and maintain a therapeutic relationship, the frequency of visits required to ensure treatment adherence, and the frequency necessary to monitor and address suicidality. Other factors which would also determine the frequency of psychotherapy visits include the severity of illness, the patient's cooperation with treatment, the availability of social supports, cost, geographic accessibility, and presence of comorbid general medical problems.

Besides the use of specific psychotherapy, all patients and their caregivers may receive psychoeducation about the illness.

**Role of Yoga and Meditation in management of depression:** Studies related to role of traditional therapies like meditation, Yoga and other techniques have been mostly published in documents of various organizations propagating that particular technique. Well-designed scientific studies to authenticate these claims need to be conducted; however, efficacy of these techniques as supportive/adjunctive therapy is widely accepted.

### TREATMENT IN CONTINUATION PHASE

The goal of continuation phase is to maintain the gains achieved in the acute phase of treatment and prevent relapse

of symptoms. The treatment algorithm to be followed is shown in figure-4. Patients who have been treated with antidepressants in the acute phase need to be maintained on same dose of these agents for 16-24 weeks to prevent relapse (total period of 6-9 month from initiation of treatment). There are evidences to support the use of specific psychotherapy in continuation phase to prevent relapse. The use of other somatic modalities (e.g. ECT) may be useful in patients where pharmacology and/or psychotherapy have failed to maintain stability in continuation phase. The frequency of visit during the continuation phase may be determined by patient's clinical condition as well as the specific treatment being provided. If maintenance phase treatment is not indicated for patients who remain stable following the continuation phase, patients may be considered for discontinuation of treatment. If treatment is discontinued, careful monitoring be done for relapse, and treatment to be promptly reinstated if relapse occurs.

### TREATMENT IN MAINTENANCE PHASE

The goal of maintenance phase treatment is to prevent recurrence of depressive episodes. On an average, 50-85% of patients with a single episode of major depression have at least one more episodes. Therefore, maintenance phase treatment may be considered to prevent recurrence. The duration of treatment may be decided keeping in view the previous treatment history and number of depressive episodes the person has had in the past. Mostly the treatment that was effective for acute and continuation phase need to be used in the maintenance phase (Figure-5). Same doses of antidepressants, to which the patient had responded in previous phase is considered. The frequency of visit for CBT and IPT can be reduced during the maintenance phase (once a month). There is no consensus regarding the duration and when to give and when not to give maintenance treatment. There is agreement to large extent that patients who have history of three or more relapses or recurrences need to be given long-term treatment.

### DISCONTINUATION OF TREATMENT

The decision to discontinue maintenance treatment may be based on the same factors considered in the decision to initiate maintenance treatment, including the probability of recurrence, the frequency and severity of past episodes, the persistence of depressive symptoms after recovery, the presence of comorbid disorders, and patient preferences. When the decision is made to discontinue or terminate psychotherapy in the maintenance phase, the manner in which this is done may be individualized to the patient's needs. When the decision is made to discontinue maintenance pharmacotherapy, it is best to taper the medication over the course of at least several weeks to few months. Such tapering may allow for the detection of emerging symptoms or recurrences when patients are still partially treated and therefore can be easily returned to full therapeutic intensity. In addition, such tapering can help minimize the risks of

**Table 11: Management of depression Special situations**

Special situation	Strategies
<b>Suicidal risk</b>	<ul style="list-style-type: none"> <li>• Risk of suicide is high in patients with depression.</li> <li>• Suicide risk to be assessed initially and over the course of treatment.</li> <li>• If the patient has suicidal ideation, intention, and/or a plan, close surveillance is necessary.</li> <li>• Whenever possible, information about presence of suicidal ideation in patient be shared with family members and they need to be instructed for various safety measures to be taken.</li> <li>• The risk of suicide in some patients recovering from depression increases transiently as they develop the energy and capacity to act on self-destructive plans made earlier in the course of their illness. However, it is not possible to predict with certainty whether a given patient will kill himself or herself.</li> <li>• A careful selection of antidepressants and ECT is an important decision to be taken by psychiatrist after considering all related factors.</li> <li>• Wherever feasible, the prescribed drugs need not be in the possession or reach of patient having suicidal intention.</li> </ul>
<b>Psychotic features</b>	<ul style="list-style-type: none"> <li>• Depression with psychotic features carries a higher risk of suicide than does major depression uncomplicated by psychosis</li> <li>• It also constitutes a risk factor for recurrent depression.</li> <li>• Depression with psychotic features responds better to treatment with a combination of antidepressants and antipsychotics than to treatment with either component alone.</li> <li>• ECT is also highly effective in depression with psychotic features.</li> </ul>
<b>Atypical features</b>	<ul style="list-style-type: none"> <li>• Atypical depressive feature include severe anxiety, vegetative symptoms of reversed biological functions (i.e., increased rather than decreased sleep, appetite, and weight), marked mood reactivity, sensitivity to emotional rejection, phobic symptoms, and a sense of severe fatigue that creates a sensation of “leaden paralysis” or extreme heaviness of the arms or legs.</li> <li>• Tricyclic antidepressants yield response rates of only 35%-50%. Response rates with MAO inhibitors are in the range of 55%-75% in patients with atypical depression. If it is determined that the patient does not wish to, cannot, or is unlikely to adhere to the dietary and drug precautions associated with MAO inhibitor treatment, the use of an alternative antidepressant is indicated.</li> <li>• The results of several studies suggest that SSRIs, MAOIs, and possibly bupropion maybe more effective treatment for atypical depression.</li> </ul>
<b>Alcohol and/or substance abuse or dependence</b>	<ul style="list-style-type: none"> <li>• Because of the frequent comorbidity of depression and alcohol or other substance abuse, efforts need to be made to obtain a detailed history of the patient’s substance use.</li> <li>• If the patient is found to have a substance use disorder, a program to ensure abstinence may be regarded as a principle priority in the treatment.</li> <li>• It is also advisable, if other factors permit, to detoxify such a patient before initiating antidepressant therapy.</li> <li>• Benzodiazepines and other sedative hypnotics carry the potential for abuse or dependence and these may be used cautiously except as part of a detoxification regimen.</li> <li>• Hepatic dysfunction and hepatic enzyme induction frequently complicate pharmacotherapy of patients with alcoholism and other substance abuse; these conditions require careful monitoring of blood levels.</li> </ul>
<b>Depression with features of obsessive-compulsive disorder Depression with panic and/or other anxiety disorders</b>	<ul style="list-style-type: none"> <li>• Clomipramine and the SSRIs have been demonstrated to be efficacious in the management of obsessive-compulsive symptoms in addition to their antidepressants efficacy.</li> <li>• Panic disorder complicates major depression in 15%-30% of the cases.</li> <li>• TCAs and SSRIs may initially worsen, rather than alleviating anxiety and panic symptoms; these medications may therefore be introduced at a low dose and slowly increased when used to treat such patients.</li> <li>• High potency benzodiazepine like alprazolam and clonazepam may sometimes be used with benefit either in combination with antidepressants or as the sole pharmacological agent for anxiety, with or without panic, coupled with milder forms of depression.</li> </ul>
<b>Depression with cognitive dysfunction (pseudo dementia)</b>	<ul style="list-style-type: none"> <li>• Signs and symptoms of cognitive inefficiency routinely accompany major depression.</li> <li>• Some patients have both depression and dementia, while others have depression that causes cognitive impairment (i.e., pseudo-dementia).</li> <li>• Several clinical features help in differentiating pseudo-dementia from true dementia. Pseudo-demented patients generally exert relatively less effort but report more incapacity than patients with true dementia. In more advanced stage, patients with dementia typically fail to recognize their cognitive failure.</li> <li>• It is important that patients with major depression with cognitive disturbance are not misdiagnosed and thereby denied the antidepressant medication or ECT.</li> <li>• Depression related cognitive dysfunction is a reversible condition that resolves with treatment of the underlying depression.</li> </ul>
<b>Dementia</b>	<ul style="list-style-type: none"> <li>• Individuals suffering from dementia need to be prescribed antidepressants which have least potential of anticholinergic effect, e.g., bupropion, fluoxetine, sertraline, and, of the tricyclic agents, desipramine or nortriptyline. Alternatively, some patients do well when given stimulants in small doses.</li> <li>• Among SSRIs, paroxetine may be avoided.</li> <li>• ECT is also effective in depression superimposed on dementia, and it may be used if medications are contraindicated, not tolerated, or if immediate resolution of the major depressive disorder episode is medically indicated (such as when it interferes with the patient’s acceptance of food).</li> </ul>
<b>Post Psychotic Depression</b>	<ul style="list-style-type: none"> <li>• Adding an antidepressant agent to the patient’s antipsychotic regimen can help in managing post-psychotic depression effectively.</li> </ul>

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Table 11: Contd...

Special situation	Strategies
<b>Depression during pregnancy or following Childbirth</b>	<ul style="list-style-type: none"> <li>• Women in childbearing age may be counseled about the risk of becoming pregnant while taking psychotropic medications.</li> <li>• Whenever possible, a pregnancy is to be planned in consultation with psychiatrist so that medication may be discontinued before conception if feasible.</li> <li>• The clinicians need to carefully weigh the risks and benefits of prescribing psychotropic agents to the pregnant patient, taking into consideration the possibilities of physical (especially during the first trimester) and behavioral teratogenesis.</li> <li>• In patients whose safety and well-being require antidepressants medications, antidepressants may be justifiably used, after the first trimester, if possible.</li> <li>• ECT may be used as an alternative treatment; the current literature supports the safety for mother and fetus, as well as the effectiveness of ECT during pregnancy.</li> <li>• Postpartum depression is to be treated according to the same principles delineated for other depressive condition.</li> <li>• However, issue of breast feeding and appropriate precautions need to be explained to patient and caregivers.</li> </ul>
<b>Seasonal depression</b>	<ul style="list-style-type: none"> <li>• Some individuals suffer annual episode of depression whose onset is in the fall or early winter, usually at the same time each year.</li> <li>• The depressive episodes frequently have atypical features such as hypersomnia and overeating.</li> <li>• The entire range of treatments for depression may also be used to treat seasonal affective disorder, either in combination with or as an alternative to light therapy.</li> </ul>
<b>Depression in elderly</b>	<ul style="list-style-type: none"> <li>• Antidepressants are effective in treatment of depression in old age.</li> <li>• The high rates of adverse effects associated with TCAs suggest that these agents must not be used as the first line agents.</li> <li>• The lower rate of adverse events in the newer antidepressants (SSRIs) makes them more acceptable. However, nortriptyline has a role in severe depression in the elderly.</li> <li>• ECT has demonstrated efficacy in treatment of old age depression with the benefit of rapid response in the severely ill with and without psychotic symptoms.</li> </ul>
<b>Depression in Children</b>	<ul style="list-style-type: none"> <li>• There are evidences that SSRIs are effective in child and adolescent depression and these are generally the first choice of drug.</li> <li>• The commonly used SSRIs include fluoxetine. Other newer antidepressants have not been adequately evaluated in childhood and use of all these classes of drugs may be used with careful monitoring.</li> <li>• Psychotherapeutic interventions like CBT and IPT have also been shown to be efficacious in children and adolescents.</li> </ul>
<b>Post- Stroke Depression</b>	<ul style="list-style-type: none"> <li>• Post Stroke Depression is a common problem seen in at least 30-40% of survivors of intra-cerebral hemorrhage.</li> <li>• Antidepressant drugs may be beneficial in managing depressive symptoms and allow faster Post Stroke rehabilitation.</li> <li>• Treatment is complicated by medical co-morbidity and by the potential for interaction with other co-prescribed drugs.</li> <li>• Fluoxetine and nortriptyline are probably the most standard and seen to be effective.</li> </ul>
<b>Cardiac disease:</b>	<ul style="list-style-type: none"> <li>• The presence of specific cardiac conditions complicates or contraindicates certain forms of antidepressant medication therapy, notably use of TCAs.</li> <li>• Cardiac history is to be carefully explored before the initiation of medication treatment. Although TCAs have been used effectively to treat depression in patients with some forms of ischemic heart disease, particular care need to be taken in using TCAs in patients with a history of ventricular arrhythmia, subclinical sinus node dysfunction, conduction defects (including asymptomatic conduction defects), prolonged QT intervals, or a recent history of myocardial infarction.</li> <li>• SSRIs, bupropion, and ECT appear to be safer for patients with preexisting cardiac disease, although the latter may require consultation with a specialist and treatment modification before use. However, there are also reports which suggest that SSRIs can also lead to arrhythmia.</li> <li>• MAOIs do not adversely affect cardiac conduction, rhythm, or contraction but may induce orthostatic hypotension and also run the risk of interacting adversely with other medications that may be taken by such patients. There is anecdotal evidence that trazodone may induce ventricular arrhythmias, but this agent may be avoided in elderly because of orthostatic blood pressure decrements.</li> <li>• Consultation with the patient's cardiologist before and during antidepressant medication treatment may be advisable and is especially advisable during any treatment for a patient who has recently had a myocardial infarction.</li> </ul>
<b>Hypertension</b>	<ul style="list-style-type: none"> <li>• Antihypertensive agents and TCAs may interact to either intensify or counteract the effect of the antihypertensive therapy.</li> <li>• The action of antihypertensive agents that block alpha receptors (e.g., prazosin) may be intensified by antidepressant medications that block these same receptors, notably the TCAs and trazodone. TCAs may antagonize the therapeutic actions of guanethidine, clonidine, or <math>\alpha</math>-methyldopa.</li> <li>• Antihypertensive, like diuretics which mainly act on kidney, may precipitate SIADH, when given along with SSRIs.</li> <li>• Concurrent antihypertensive treatment, especially with diuretics, increases the likelihood that TCAs, trazodone, or MAOIs will induce symptomatic orthostatic hypotension.</li> <li>• <math>\beta</math> Blockers, especially propranolol, may be a cause of depressive disorder in some patients.</li> <li>• Dose-dependent elevations in blood pressure with venlafaxine are usually mild, although more severe elevations have been observed, making this agent less preferable in patients with hypertension.</li> </ul>

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<b>Special situation</b>	<b>Strategies</b>
<b>Diabetes mellitus</b>	<ul style="list-style-type: none"> <li>• SSRIs may reduce serum glucose by up to 30% and cause appetite suppression, resulting in weight loss.</li> <li>• Fluoxetine may be avoided, owing to its increased potential for hypoglycaemia, particularly in patients with non-insulin dependent diabetes. If fluoxetine is prescribed, the patient should be advised of the need to monitor serum glucose levels regularly.</li> <li>• TCAs are more likely to impair diabetic control as they increase serum glucose levels by up to 150%, increase appetite (particularly carbohydrate craving) and reduce the metabolic rate. They are generally considered safe unless the diabetes is very poorly controlled or is associated with significant cardiac or renal disease.</li> <li>• Antidepressants such as amitriptyline, imipramine, duloxetine and citalopram are also used to treat painful diabetic neuropathy.</li> </ul>
<b>Asthma</b>	<ul style="list-style-type: none"> <li>• Antidepressant medications except MAOI may be used for patients with asthma without fear of interaction. Other antidepressant like SSRIs, TCAs, etc., may be used for patient with asthma without any apprehension about drug interaction.</li> </ul>
<b>Glaucoma</b>	<ul style="list-style-type: none"> <li>• Antidepressants that cause or exacerbate acute close angle glaucoma include medications with anticholinergics, serotonergic or adrenergic properties.</li> <li>• TCAs have the greatest anticholinergic properties,</li> <li>• SSRIs and SNRIs by virtue of their action on serotonin receptor can also cause mydriasis and thereby can produce papillary block.</li> <li>• Antidepressants lacking anticholinergic and serotonergic activity (bupropion) may be preferred.</li> <li>• Benzodiazepines (Diazepam) have mild anticholinergics properties.</li> </ul>
<b>Obstructive uropathy</b>	<ul style="list-style-type: none"> <li>• Prostatism and other forms of bladder outlet obstruction are relative contraindications to the use of antidepressant medication compounds with antimuscarinic effects.</li> <li>• Benzodiazepines, trazodone, and MAOIs may also retard bladder emptying.</li> <li>• The antidepressant medications with the least propensity to do this are SSRIs, bupropion, and desipramine.</li> </ul>
<b>Parkinson's disease</b>	<ul style="list-style-type: none"> <li>• Bupropion, exerts a beneficial effect on the symptoms of Parkinson's disease in some patients but may also induce psychotic symptoms, perhaps because of its agonistic action in the dopaminergic system.</li> <li>• MAOIs (other than selegiline, also known as L-deprenyl, a selective type B MAOI is recommended in the treatment of Parkinson's disease) may adversely interact with L-dopa products.</li> <li>• Selegiline loses its specificity for MAO-B in doses greater than 10 mg/day and may induce serotonin syndrome when given in higher doses in conjunction with serotonin-enhancing antidepressant medications.</li> <li>• There is no evidence favoring any particular antidepressant medication from the standpoint of therapeutic efficacy in patients with Parkinson's disease complicated by depressive disorder.</li> <li>• The theoretical benefits of the antimuscarinic effects of some of the TCAs in the treatment of patients with depressive disorder with Parkinson's disease are offset by the memory impairment that may result.</li> <li>• ECT exerts a transient beneficial effect on the symptoms of idiopathic Parkinson's disease in many patients.</li> <li>• Amoxapine, an antidepressant medication with dopamine-receptor blocking properties, may be avoided for patients who have Parkinson's disease.</li> <li>• Lithium may in some instances induce or exacerbate parkinsonian symptoms.</li> </ul>
<b>Malignancy</b>	<ul style="list-style-type: none"> <li>• In treatment of depression in subjects with malignancy, SSRI are considered to be the first line drugs. The advantage of SSRI is that they can act as effective adjunct analgesic drugs, especially in neuropathic pain. Disadvantages of SSRI are drug-drug interaction with drugs that are metabolized by CYP450/3A4 (e.g. cyclophosphamide, doxorubicin). Fluoxetine, may be used with caution especially in patients with hepatic insufficiency, since it has a long half-life.</li> <li>• TCAs are also good adjunct analgesics. But the disadvantages with TCAs are anticholinergic side effects and orthostatic hypotension. They can also worsen their side effects of drugs like opioids (e.g. constipation and dry mouth) which are often needed for pain control.</li> <li>• Psychostimulants, with their rapid onset of action have some advantages for depressed cancer patients in the sense of promoting a sense of well-being, decreasing fatigue, stimulating appetite, potentiating the analgesic effect of opioids and decreasing opioid induced sedation.</li> <li>• The goal of psychological treatment in depressed patients with cancer is to reduce emotional distress, improve morale, coping ability, self-esteem and sense of control.</li> </ul>
<b>Drug induced depression</b>	<ul style="list-style-type: none"> <li>• If medication induced depression is suspected, the suspected drug should be discontinued if possible and replaced with another agent less likely to induce depression.</li> <li>• When this is not possible or when discontinuation does not result in remission of the depressive symptoms, pharmacotherapy for the depression may be considered.</li> </ul>

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Table 11: Contd...

Special situation	Strategies
Liver disease	<ul style="list-style-type: none"> <li>• Liver impairment affects basic elements of medication pharmacokinetics, from absorption to metabolism, distribution to elimination, changing drug levels, duration of action, and efficacy.</li> <li>• Most antidepressants are highly protein-bound- except, venlafaxine, and methylphenidate.</li> <li>• In liver failure, a reduction in albumin and alpha1-acid-glycoprotein production, along with altered protein-binding, leads to higher levels of free pharmacologically-active drug. This is offset by a compensatory increase in the rate of hepatic metabolism, and this is especially important for drugs with low intrinsic clearance.</li> <li>• Most antidepressants are highly lipid-soluble and require hepatic metabolism (biotransformation into more polar compounds) to allow them to be cleared from the body in urine or bile.</li> <li>• Antidepressants can also be divided into two major categories of clearance, determined by their enzyme affinity. Flow-limited drugs have high hepatic extraction, and their hepatic clearance is dependent on the rate of delivery of the drug to the liver. TCAs undergo significant first pass metabolism of greater than 50% after oral administration.</li> <li>• Drugs with low hepatic-enzyme affinity (e.g., paroxetine) are metabolized more slowly, as enzyme saturation is the rate limiting step. The severity of impairment rather than the underlying aetiology is the most important factor to consider in prescribing for this group. Renal function may also be affected.</li> <li>• As the risk of drug toxicity increases with disease severity, lower starting and total doses of medication are recommended (starting dose -about one forth that of adults).</li> </ul>
Renal disease	<ul style="list-style-type: none"> <li>• In this group of patients, TCAs are probably safer than SSRIs.</li> <li>• The degree of renal impairment rather than the cause is most important.</li> <li>• Renal impairment may be present without a raised creatinine level. TCAs metabolites are excreted by the kidneys, hence accumulation may occur. Of the SSRIs, sertraline is not recommended by its manufacturers in renal failure.</li> <li>• Fluoxetine, citalopram and paroxetine may be started at very low dose in patients with a glomerular filtration rate of at least &gt;10 ml/min.</li> <li>• Lithium may only be prescribed if absolutely necessary, at low doses, on alternate days, with frequent checking of serum levels.</li> </ul>
Perioperative period	<ul style="list-style-type: none"> <li>• TCAs may preferably be stopped prior to surgery. SSRIs and MAOI can interact with pethidine, pentazocine, and dextromethorphan, at the pharmacodynamics levels and lead to serotonin syndrome, therefore such drugs may be avoided during the perioperative period. However, SSRIs may not be discontinued in order to prevent anesthetic interactions, except when the SSRI is used in combination with aspirin or a Non-steroidal anti-inflammatory drugs and when the SSRI is used in patients over 80 years of age. In these patients, the balance of risks of withdrawal and bleeding is to be discussed with patients. Because abrupt discontinuation can cause serious withdrawal symptoms, the drugs may be gradually discontinued over few days to 2 weeks before surgery.</li> <li>• Lithium can contribute to hemodynamic instabilities, interfere with sodium and potassium metabolism, and the renal excretion of lithium can be reduced in presence of renal complications. The physical risk of intoxication, with its detrimental and fatal risks for the central nervous system, is unacceptable. Therefore, lithium discontinuation is recommended. Lithium can be stopped at once because no withdrawal symptoms occur.</li> <li>• When, postoperatively, the patient is hemodynamically stable, is able and allowed to drink, and is not on new, potentially interfering drugs, the medication may be restarted gradually.</li> </ul>

antidepressant medication discontinuation syndromes. Discontinuation syndromes have been found to be more frequent after discontinuation of medications with shorter half-lives, and patients maintained on short-acting agents may be given even longer, more gradual tapering. Paroxetine, venlafaxine, TCAs, and MAOIs tend to have higher rates of discontinuation symptoms while bupropion-SR, citalopram, fluoxetine, mirtazapine, and sertraline have lower rates. The symptoms of antidepressants discontinuation include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances (e.g., electrical sensations) and hyperarousal (agitation). If the discontinuation syndrome is mild, reassurance may be sufficient. If mild to moderate, short-term symptomatic treatment (analgesics, antiemetics, or anxiolytics) may be beneficial. If it is severe, antidepressant are to be reinstated and tapered off more slowly.

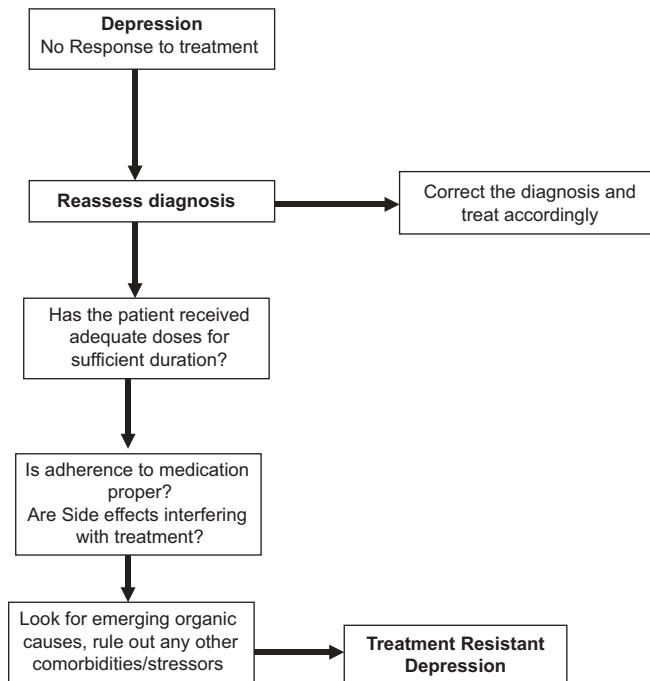
After the discontinuation of active treatment, patients **should** be reminded of the potential for a depressive relapse. Patient may be again informed about the early

signs of depression, and a plan for seeking treatment in the event of recurrence of symptoms may be formulated. Patients may be monitored for next few months to identify relapse. If a patient suffers a relapse upon discontinuation of medication, treatments need to be promptly reinitiated. In general, the previous treatment regimen to which the patient responded in the acute and continuation phase are to be considered.

## MANAGEMENT OF TREATMENT RESISTANCE DEPRESSION

Initial treatment with antidepressant medication fails to achieve a satisfactory response in approximately 20%-30% of patients with depressive disorder. In some cases the apparent lack of treatment response is actually a result of faulty diagnosis, inadequate treatment, or failure to appreciate and remedy coexisting general medical and psychiatric disorders or other complicating psychosocial factors. Adequate treatment for at least 4-6 weeks is

necessary before concluding that a patient is not responsive to a particular medication. First step in care of a patient

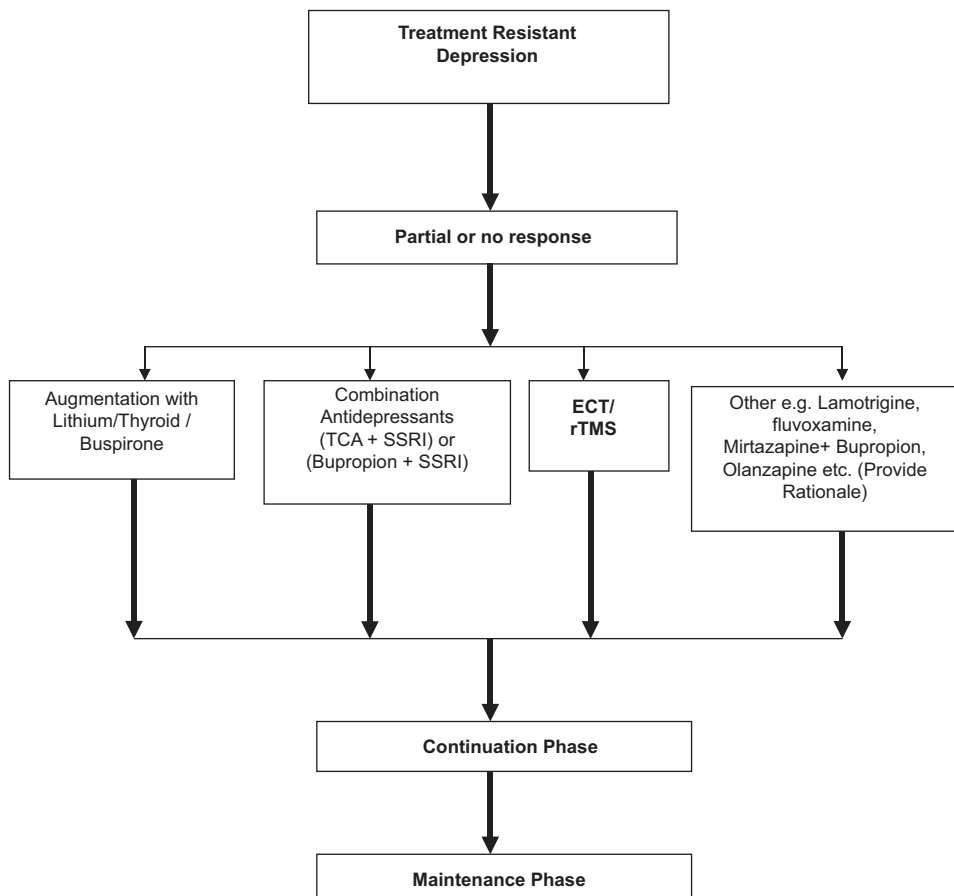


**Figure 6:** Algorithm for arriving at the diagnosis of Treatment Resistant Depression

who has not responded to medication is carrying out a thorough review and reappraisal of the psychosocial and biological information base, aimed at revalidating the diagnosis and identifying any neglected and possibly contributing factors, including the general medical problems, alcohol or substance abuse or dependence, other psychiatric disorders, and general psychosocial issues impeding recovery. Algorithm for arriving at the diagnosis of treatment resistant depression is given in figure-6.

Some clinicians require two successive trials of medications of different categories for adequate duration before considering treatment resistant depression (TRD). Management of TRD involves addition of an adjunctive agent, combining two antidepressants, addition of ECT or other somatic treatments like rTMS. Algorithm for management of TRD is given in figure-7.

**Addition of an adjunct to an antidepressant:** Lithium is the drug primarily used as an adjunct; other agents in use are thyroid hormone and stimulants. Opinion differs as to the relative benefits of lithium and thyroid supplementation. It is reported that lithium is useful in over 50% of antidepressant nonresponders and is usually well tolerated. The interval before full response to adjunctive lithium is said to be in the range of several days to 3 weeks.



**Figure 7:** Algorithm for management of Treatment Resistant Depression



If effective and well tolerated, lithium may be continued for the duration of treatment of the acute episode. Thyroid hormone supplementation, even in euthyroid patients, may also increase the effectiveness of antidepressant treatment. The dose proposed for this purpose is 25 µg/day of triiodothyronine increased to 50 µg/day in a week.

**Simultaneous use of multiple antidepressants:** Depression is a chronic disabling condition in case patient does not respond to single drug regimen; clinicians may use combination/polytherapy with close monitoring of side effects and drug interaction profile. Combinations of antidepressant carry a risk of adverse interaction and sometimes require dose adjustments. Use of a SSRI in combination with TCA has been reported to induce a particularly rapid antidepressant response. However, fluoxetine added to TCAs causes an increased blood level and delayed elimination of the TCA, predisposing the patient to TCA drug toxicity unless the dose of the TCA is reduced. Another strategy involves combined use of a tricyclic antidepressant and a MAO inhibitor, a combination that is sometimes effective in alleviating severe medication-resistant depression, but the risk of serotonin syndrome necessitates careful monitoring.

**Electroconvulsive therapy:** Response to ECT is generally good and the response rates are like any form of antidepressant treatment and it may be considered in virtually all cases of moderate or severe major depression who do not respond to pharmacologic intervention. Approximately 50% of medication resistant patients exhibit a satisfactory response to ECT. Lithium may be discontinued before initiation of ECT, as it has been reported to prolong postictal delirium and delay recovery from neuromuscular blockade.

#### Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive transcranial magnetic stimulation (rTMS; a type of TMS that occurs in a rhythmic and repetitive form) has been put forward as a new technique to treat this debilitating illness. Current evidence suggests that rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) is a promising treatment strategy for depression, but not all patients show a positive outcome. Current clinical outcome studies report rather modest superiority compared with placebo (sham). To date, it remains unclear which TMS parameters, such as

stimulation duration and intensity, can produce the most benefits. Moreover, there is no consensus of the exact brain localization for individual coil placement.

#### MANAGEMENT OF SPECIAL CONDITIONS

Clinicians often encounter certain clinical situations which either require special attention or can influence treatment decisions. Management of these situations is summarized in table-11.

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