

Clinical Practice Guidelines on Treatment Emergent Sexual Dysfunctions

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EXECUTIVE SUMMARY

Problem statement

Treatment emergent sexual dysfunction (TESD) is one of the most unrecognized adverse effects of psychotropic treatment and non-psychotropic treatment. It affects 25-80% of patients on antidepressants and 16-60% of patients on antipsychotics. Many non-psychotropic medications used for the treatment of common medical conditions have also been implicated in the occurrence of TESD. It is one of the chief causes of medication non-adherence and treatment discontinuation across all psychiatric diagnoses.

Pathophysiology

TESD arises from disturbance of the dopaminergic, serotonergic, adrenergic, cholinergic and hormonal axes regulating the sexual response cycle. SSRIs and SNRIs primarily cause TESD by 5HT_{2A/2C} receptor overstimulation and resulting dopamine suppression. Antipsychotics act via tuberoinfundibular D₂ blocking, leading to hyperprolactinemia and resulting hypogonadism. Mood stabilizers like carbamazepine act by enzyme induction, thereby reducing sex hormone bioavailability, while sodium valproate is associated with Polycystic Ovarian Syndrome (PCOS). Understanding these mechanisms is imperative to rational agent selection and targeted management of adverse sexual side effects.

Assessment

ASEX is the recommended minimum screening tool at every clinical contact. The PRSexDQ specifically attributes dysfunction to medications. The IIEF and FSFI are gold-standard domain specific assessment for male and female patients respectively. Serum prolactin, sex hormone panel (testosterone, LH, FSH, estradiol) and thyroid function should be a necessary part of baseline and monitoring investigations for all antipsychotic treated patients.

Management of antidepressant related sexual dysfunction

Most cases of TESD do not resolve spontaneously even after 6 months, and are often underreported. Hence routine screening is essential. Non-drug measures like psychoeducation, lifestyle changes, specific techniques like Kegel exercises, sensate focus, start-stop/ squeeze techniques for premature ejaculation, sex therapy or CBT can be tried. Drug strategies include waiting for tolerance in mild cases, reducing the dose, switching to a lower risk antidepressant (e.g., bupropion, agomelatine, mirtazapine, vortioxetine), or augment with agents like bupropion, buspirone, or PDE-5 inhibitors.

Management of antipsychotic associated sexual dysfunction

General principles and non-pharmacological treatment are similar to that of antidepressant induced sexual dysfunction. Ruling out hyperprolactinemia is primary, apart from excluding co-offending agents or specific comorbidities causing sexual dysfunction. Waiting for spontaneous remission is not advisable. Reducing the dose of antipsychotic is not always a feasible option, due to nonlinear relationship between dosage and sexual side effects. Moreover, reducing dose of antipsychotics can cause relapse of psychotic symptoms.

For all antipsychotic associated sexual dysfunction, the best recommended practice is to switch to aripiprazole. The second level of evidence stands for adding aripiprazole to the existing treatment

regime, or using olanzapine <15 mg/ day, or quetiapine/ ziprasidone. For erectile dysfunction, PDE5 inhibitor addition and for vaginal dryness, use of vaginal lubricants have second level of evidence.

Management of mood stabilizer associated sexual dysfunction

Robust literature is lacking. Most evidence is for switching or adding lamotrigine to existing therapy. Addition of aspirin was shown to be beneficial in lithium TESD in a small RCT.

TESD associated with non-psychotropic medications

Cardiovascular drugs, (especially non selective and older generation beta blockers, thiazide diuretics and loop diuretics, digoxin and centrally acting agents), antidiabetic and lipid lowering agents, anticancer medications, opioid analgesics, contraceptives, Gonadotropin-releasing hormone (GnRH) analogues, antiretroviral therapy, steroids, 5 alpha reductase inhibitors, anti fungals and immunosuppressive drugs have all been implicated in the development of TESD. Management strategies may include modification of contributing factors, dose optimization, switching to an alternative medication with a more favorable sexual adverse-effect profile, or addition of an appropriate symptomatic treatment.

To sum it up, management is stepwise and tailored to patient needs- starting with psychoeducation and lifestyle measures, escalating to dose adjustment or switching, and implementing augmentation strategies for patients where switching is not feasible. The whole process should follow a collaborative approach for better long-term outcome.

Introduction

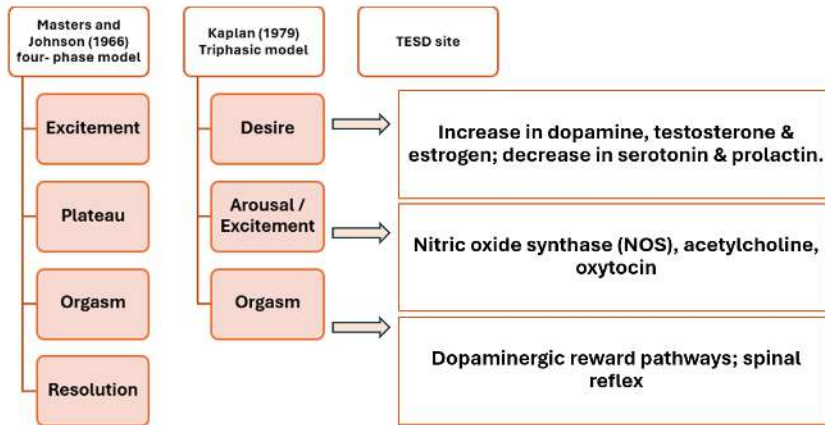
Sexual health is a basic domain of human well-being, and inseparable from overall health and quality of life. Psychotropic medications, though transformative in reducing the overall burden of mental illness, are associated with a significant iatrogenic challenge: Treatment emergent sexual dysfunction (TESD). The term encompasses a wide spectrum of medication induced impairments spread across the phases of sexual cycle, including decreased libido (hypoactive sexual desire disorder), impaired arousal (erectile dysfunction in men; reduced lubrication and genital engorgement in women), delayed or absent orgasm (anorgasmia, delayed ejaculation), and ejaculatory dysfunction.

TESD is a substantial and common burden in psychiatric practice. The fifth International Consultation on Sexual Medicine (ICSM, 2024) reported that it affects 25-80% of patients on antidepressants and 16-60% of those on antipsychotics.^[1]

The clinical consequences of TESD extend far beyond patient distress. They are one of the most common reasons for medication non-adherence. As compared to other side effects associated with psychotropics like weight gain, sedation and dry mouth, sexual side effects have a tendency to persist. A review by Montejo et al^[2] reaffirmed that TESD tends to persist over time and are underrecognized by clinicians and less investigated in clinical trials. This is due to a mutual reluctance to discuss sexual functions on the part of the patients and the clinicians.^[3]

Pathophysiology

Masters and Johnson developed the four-phase model of the sexual cycle- excitement, plateau (where the physiological changes of excitement are continued and intensified), orgasm, and physiological resolution. Helen Singer Kaplan proposed the three-phase model, where desire is the first phase followed by excitement and orgasm. Desire incorporates the psychological motivational factors that are central to initiation of physiological responses, since problems of desire (low libido) are different from problems of physiological arousal. The phase of resolution was not described explicitly in Kaplan's model for the purpose of clinical simplicity.



Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Noradrenaline Reuptake Inhibitors (SNRI) cause excess stimulation of the 5HT_{2A} and 2C receptors in the limbic system and hypothalamus, which leads to a tonic inhibition of dopamine release (damping sexual motivation and reward) and additionally inhibit Nitric Oxide Synthase (NOS) in the genital tissue, decreasing vasodilatory arousal responses. These side effects may be dose dependent and show some response to reduction in dose. ^[5,6]

5HT_{2C} activation also causes elevation of prolactin, leading to suppression of libido. Peripherally, delayed ejaculatory reflex at the level of sacral spinal cord may lead to delayed or absent orgasm. ^[7]

Tricyclic antidepressants (TCA) cause sexual dysfunction through diverse pathways: Serotonergic mechanism, which is shared with SSRIs, anticholinergic action (leading to genital vasoconstriction and impaired genital lubrication), antihistaminergic activity (causing sedation) and alpha blockade (damping erection and ejaculation). Clomipramine particularly has very high rates of TESS. Genetic susceptibility studies show that a higher SERT affinity leads to a higher risk of TESS, while a higher 5HT_{2C} affinity leads to a lower risk of TESS. ^[8]

CYP2C19 metabolizer phenotypes, 5HT_{2A}, SLC6A4, glutamatergic receptor polymorphisms also influence TESS susceptibility. ^[9,10]

Antidepressants with low propensity for TESS include bupropion, mirtazapine, agomelatine and vortioxetine. Bupropion may enhance sexual function in addition to effects on smoking cessation. ^[11]

Drug	Prevalence of TESS	Phase of sexual response
Moclobemide	0.22%	Desire, orgasm, arousal
Agomelatine	0.25%	Desire, orgasm
Bupropion	0.75%	Desire, orgasm, arousal
Mirtazapine	2.32%	Desire, orgasm, arousal
Fluvoxamine	3.27%	Desire, orgasm, arousal
Escitalopram	3.44%	Desire, orgasm, arousal
Duloxetine	4.36%	Desire, arousal

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Imipramine	7.24%	Desire, orgasm, arousal
Fluoxetine	15.59%	Desire, orgasm, arousal
Paroxetine	16.68%	Desire, orgasm, arousal
Citalopram	20.27%	Desire, orgasm, arousal
Venlafaxine	24.82%	Desire, orgasm, arousal
Sertraline	27.43%	Desire, orgasm, arousal

Table 1: Phases of sexual response cycle affected by antidepressants ^[12]

Antipsychotics

Mechanism of action of antipsychotic induced SD^[13]

- Dopamine receptor antagonism leads to inhibition of motivation and reward and decreased desire. First-generation antipsychotics (haloperidol, pimozide, trifluoperazine) and risperidone can blunt sexual desire, inhibit reward and cause anorgasmia or erectile dysfunction independent of prolactin by direct dopaminergic suppression in the mesolimbic pathway. ^[13]
- Dopamine D2 receptor antagonism (tubero-infundibular pathway) leads to hyperprolactinemia and thereby causes decreased desire, impaired arousal, impaired orgasm.
- Partial D2 agonists like aripiprazole, brexpiprazole and cariprazine have favorable sexual side effects profile. ^[14]
- Histamine receptor antagonism causes sedation and impairs arousal.
- Cholinergic receptor antagonism leads to reduced peripheral vasodilation, thereby causing erectile dysfunction. The anticholinergic effects of first-generation antipsychotics like chlorpromazine and add-on drugs like trihexyphenidyl are noted for causing erectile dysfunction, decreased genital sensations, as well as delayed or retrograde ejaculation.
- α -adrenergic antagonism leads to reduced peripheral vasodilation, causing priapism, decreased erection/lubrication, abnormal ejaculation.
- Serotonergic effects mediated by increased stimulation of 5HT_{2A/2C} receptors by second generation antipsychotics like risperidone or quetiapine can lead to decrease in libido, as well as anorgasmia.

Prolactin and antipsychotics

- Prolactin raising antipsychotics – Amisulpride, haloperidol, paliperidone, risperidone, other typical antipsychotics
- Prolactin sparing antipsychotics – Aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone

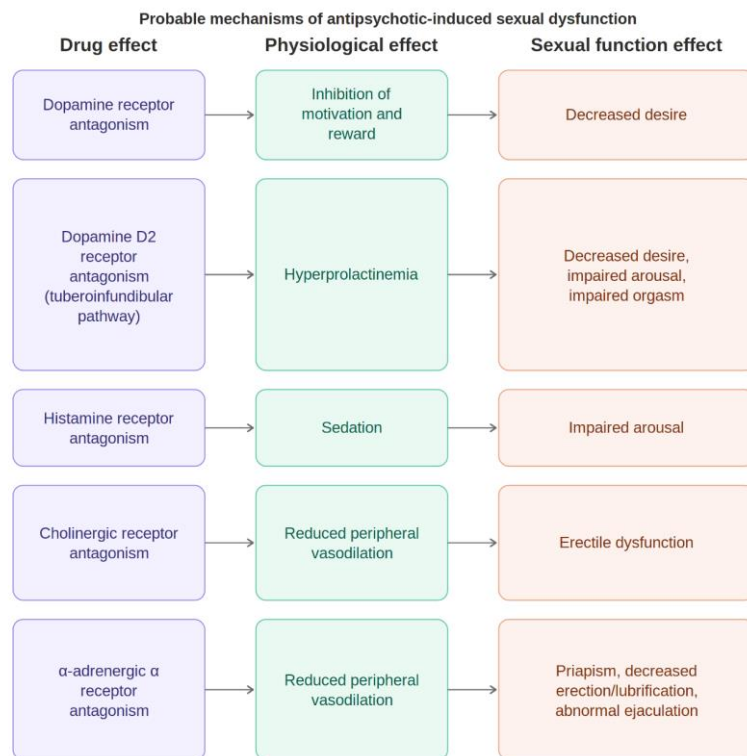


Figure 2. Summary of probable mechanisms of antipsychotic induced sexual dysfunction

Mood stabilizers

Lithium- It has been shown to cause suppression of sexual desire, hypoarousal symptoms, erectile dysfunction and orgasmic dysfunctions. Though the exact mechanisms remain unclear, it has been postulated that lithium can cause sexual dysfunction by its effects on neuroendocrine signaling, neurotransmitter modulation, and hormonal balance, which can interfere with normal erectile physiology. Additionally, it causes thyroid dysfunction, which itself may hamper sexual function.^[2] Carbamazepine is an enzyme inducer, and may increase hepatic metabolism of sex hormones, lowering their bioavailability. Valproate is associated with increased risk of Polycystic Ovary Syndrome (PCOS) in women, which alters the hormonal environment required for optimal female sexual function.^[15]

Lamotrigine is enzyme neutral in its kinetics and causes least TESD.^[15] Gabapentin and topiramate can cause difficulties in orgasmic in both men and women, and has also been shown to be associated with reduced libido in women.^[16-18]

Benzodiazepines

The literature on sexual side effect of benzodiazepines is limited, and insufficient to draw any definitive conclusions.^[19]

Some studies do show evidence for sexual dysfunction associated with benzodiazepines, but the evidence is conflicting.^[20]

The main postulated mechanism is GABAergic inhibition of central arousal and dopaminergic reward circuits. A 1992 study by Ghadirian and colleagues found that coadministration of benzodiazepines

with lithium was associated with substantially higher rates of sexual dysfunction (49%) compared with lithium alone (14%).^[21]

Assessment

The basic outlines of assessment of TESD are given in Box 1 below:

Box 1
• Spontaneous reporting has low validity • Structured clinician-initiated interviews with validated instruments captures reliable information • Baseline sexual function assessment should be performed before starting any psychotropic, and should be repeated at follow up appointment • Assessment should inquire specifically into each phase of the sexual cycle (desire, arousal, orgasm, resolution) • Specific inquiry into patient's subjective distress regarding sexual dysfunction. • Use of gender affirming, non-judgmental language preferably adapted to the patient's cultural context. • Temporal relationship between medicine initiation and symptom onset to address causality.

The salient features of tools used in the assessment of TESD are given in Table 2.

Instrument	Gender	Domains	Number of items	Comments
ASEX	Male & female	Drive, arousal, lubrication/erection, orgasm, satisfaction	5	Brief, validated, wide usage. Cutoff ≥ 19 s/o Sexual dysfunction.
CSFQ-14	Male & female	Desire, arousal, orgasm	14	Gender specific scoring, sensitive to drug induced changes
PRSexDQ	Male & female	Desire, arousal/erection/lubrication, orgasm/ejaculation, global satisfaction	6	TESD specific, clinician administered
IIEF-15/IIEF-5	Male	Erectile function, orgasmic function, desire, satisfaction	15/5	Gold standard for male erectile dysfunction.
FSFI	Female	Desire, arousal, lubrication, orgasm, satisfaction, pain	19	Gold standard for female sexual dysfunction. Cutoff < 26.55 ; covers 6 domains

ASEX: Arizona Sexual Experience Scale; CSFQ: Changes in Sexual Functioning Questionnaire; PRSexDQ: Psychotropic Related Sexual Dysfunction Questionnaire; IIEF: International Index of Erectile Function; FSFI: Female Sexual Function Index

Table 2-: Tools used in the assessment of TESD.

The ASEF is recommended as a universal first line screening tool for both male and female patients due to its simplicity, validated cutoff scores, and sensitivity across different psychotropic drug types.

^[22] The PRSexDQ was developed by Montejó and colleagues specifically for antidepressant and

antipsychotic associated sexual dysfunction.^[23] The IIEF and FSFI are gold standards for more detailed domain specific sexual dysfunction in male and female patients.^[24, 25]

Biological assessments are mandatory in evaluation of TESD and include evaluation of serum prolactin (for antipsychotic associated sexual dysfunction). Sex hormone analysis (testosterone, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), estradiol), thyroid profile and cardiovascular risk factors are indicated based on specific case requirements. All of this may have causative or contributory role in TESD and direct management protocol.

The basic outlines of what needs to be asked by the clinicians have been enumerated in Table 3:

Domain	Question	Comments
Baseline sexual function	How was your sexual function prior to starting medication?	Documenting baseline will avoid confusion between TESD and preexisting sexual disorder
Desire	Have you noticed any change in your desire after starting/ adjusting this medication?	Desire, arousal and orgasm can be affected independently,
Arousal	Any difficulty in erections/ vaginal lubrication after starting/adjusting this medication?	Ask both about physiological and subjective arousal
Orgasm/ ejaculation	Have you noticed any delay/ difficulty to reach orgasm/ ejaculate?	Sensitive marker for SSRI/SNRI related TESD.
Satisfaction/ distress	How satisfied are you with your conjugal life, and how much does this problem bother you?	Distress warrants intervention, not just presence of mild symptoms.
Follow-up assessment	Re-administer a validated screening tool (ASEX, PRSexDQ) rather than reliance on patient self-report.	Use the same tool at each follow up visit for better comparability.

Table 3: Practical tips for clinicians: What to ask? ^[11, 22,23]

Management Strategies

Management Strategies for Treatment Emergent Sexual Dysfunction (TESD)

For management of TESD, it is recommended that ^[1]-

- Practitioners should be aware of the risk of TESD and the interplay of various psychosocial factors, illness related factors and other medical or physical causes that can influence it.
- Clinicians should remain vigilant and consistently assess for treatment emergent sexual dysfunction related to particular psychotropic agents throughout the entire course of treatment.

General Principles

Box 2	Prevent TESD in vulnerable population – use agents with low probability of incidence of SD Routine assessment in clinical practice for emergence of TESD Intervene once TESD occurs and is a concern for patient/partner
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Management of Antidepressant related TSED ^[11,26]

Box 3

Non- Pharmacological interventions

- Psychoeducation/sex education - Psychoeducation about possible adverse sexual side effects when initiating psychotropics as well as the potential sexual dysfunction associated with the disease process itself. If sexual side effects occur, address concerns about reversibility, impact on relationship and discuss management options which will be reassuring for the patient and partner.
- Clarify myths/misconceptions about sexuality
- General interventions to improve sexual health – healthy lifestyle, weight management, stress management, treatment of any substance addiction, focusing on partner intimacy and interpersonal relationships, physical exercise, relaxation exercises. Physical exercise has been shown to improve desire and sexual satisfaction in women on antidepressants ^[27].
- General techniques to improve sexual functioning like Kegels/ exercises and Sensate focus can be beneficial ^[26].
- For Premature ejaculation, start-stop technique and squeeze technique can be employed ^[26].

Specific psychotherapy ^[26]

- Dual sex therapy
- CBT
- Mindfulness based therapy

Pharmacological interventions

Waiting for spontaneous remission (adaptation/ tolerance) – This is a commonly used strategy by clinicians as some patients may report partial or complete improvement in treatment emergent sexual dysfunction within weeks to few months. However, clinicians need to be vigilant and assess sexual functioning in every follow-up as recent literature indicates that most patients (80%) do not report any significant improvement in sexual dysfunction after six months of treatment and unless specifically enquired undetected sexual dysfunction may persist and lead to nonadherence to treatment. ^[11] This strategy can be used in patients who have demonstrated treatment response to the chosen antidepressant, have mild sexual dysfunction with no significant distress or impairment (e.g. patients who are not sexually active) or in whom medications are not planned for long term. Patient preference is of paramount importance and any decision needs to be taken in a collaborative manner after comprehensive psychoeducation about the nature of sexual dysfunction, reversibility of side effects and options available to mitigate the side effect and pros and cons of the treatment.

Reducing the dose or withdrawing antidepressant – There is some evidence that suggests sexual dysfunction caused by SSRIs correlates with dose. ^[24] However, individual variations are common, with TSED occurring in some individuals at low doses. Reducing the dose of an antidepressant caused significant improvement in TSED in a prospective, multicentric study of 344 patients under treatment with SSRIs. ^[28] Abrupt dose reduction can precipitate relapse of depressive symptoms or discontinuation syndrome and this aspect should be considered. Patients on higher doses of medication who are in

remission can be considered for gradual dose reduction with careful monitoring of symptom severity, keeping in mind not to titrate below the minimum effective dose. When dose reduction is being considered, psychotherapy can be utilized as an adjunctive therapy. A recent concept talks about Post SSRI Sexual Dysfunction (PSSD), where treatment emergent sexual dysfunction persists even after discontinuation of SSRIs. It is proposed that for PSSD, the diagnostic criteria include prior treatment with a serotonin reuptake inhibitor and an enduring change in somatic(tactile) or erogenous (sexual)genital sensation after treatment stops. It is present for ≥ 3 months after stopping treatment and may be accompanied by persistent reduction or loss in desire, erectile dysfunction or difficulty in achieving orgasm.^[29]

Drug Holiday- This strategy is not usually recommended as it carries a high risk of relapse. Here antidepressants are withheld or used at a lower dose few days before anticipated sexual activity. This can only be used for drugs with a short half -life and in those patients in whom the depression is mild and sexual dysfunction is debilitating.

Switching to a drug with less propensity for causing sexual dysfunction – This is a common strategy employed by clinicians, the rationale being to switch to an effective and safe antidepressant with a different mechanism of action which has lower risk of TESD. Switching from a SSRI to a non-serotonergic or partially serotonergic class of medication can improve TESD.^[11] The commonly preferred drugs for switching are-

Non serotonergic drugs^[11,26]

Bupropion- It acts by norepinephrine and dopamine transporter inhibition and is effective at a dosage of 150-450mg/day. It is commonly used due to encouraging results from multiple studies. Increased risk of seizures, exacerbation of anxiety and sleep disturbances can occur with bupropion and needs vigilance. Bupropion may not be effective when used as the sole antidepressant and studies have looked at combination of bupropion with SSRI to reduce TESD where switching is not feasible and it was found that combining bupropion with SSRIs or venlafaxine improved the sexual functioning.^[30, 31]

Agomelatine – It has a noradrenergic and dopaminergic effect due to MT1 and MT2 melatonin receptor agonism and 5HT2C receptor antagonism. The dose ranges from 25- 50 mg/day. Nausea and headache are commonly reported adverse effects. RCTs comparing agomelatine to paroxetine^[32] and escitalopram^[33] have reported reduced occurrence of TESD with agomelatine while another study comparing agomelatine to venlafaxine demonstrated comparable efficacy as antidepressant and reduced incidence of TESD with agomelatine.

Mirtazapine - Mirtazapine is a noradrenergic and serotonergic dual-action AD which acts by stimulation of 5HT1 postsynaptic receptors and blockade of 5HT2 and 5HT3 postsynaptic receptors and $\alpha 2$ blockade. It is used at dose of 15- 45 mg/day. It causes prominent sedation and weight gain. Improvement in TESD while maintaining antidepressant efficacy after switching to mirtazapine from other ADs has been reported in observational studies.^[34,35]

Partially serotonergic drugs^[11,26]

In certain conditions switching to a non-serotonergic drug may not be efficacious and in these cases, partially serotonergic medication may be considered. Desvenlafaxine works by norepinephrine and serotonin transporter inhibition, is well tolerated and has good efficacy as antidepressant. TESD with desvenlafaxine can occur at higher doses (above 100mg/day) but there is reduced likelihood at 50 mg/day.^[36] Observational studies have reported improvement in TESD after switching to desvenlafaxine.^[37,38]

Vortioxetine has a multimodal mechanism of action and low serotonergic effect. In two controlled trials where an SSRI was switched to either escitalopram or vortioxetine, significant improvement in sexual functioning was demonstrated with vortioxetine and it had similar efficacy.^[39,40]

Other Antidepressants^[11,26]

Moclobemide- It is a reversible monoamine oxidase type A inhibitor used at a dosage of 300-600mg/day. Switching to moclobemide has been shown to improve TESD and there are reports of stimulating effects

on sexual functioning with moclobemide use. ^[41] However, moclobemide requires a long washout period when switching and its long-term utility is questionable.

Low incidence of TESD has been reported with reboxetine, trazodone, maprotiline and mianserin but there is limited literature on the utility of switching to these agents.

Augmentation/Add-on strategy

Here, another agent is added to the existing treatment regimen, the rationale being to reduce the dose of the offending drug and thereby bring about improvement in TESD.

Box 4

- **Add-on agents for improving anti-depressant induced anorgasmia ^[11]**
 - Cyproheptadine (4-8 mg/day) - 5HT antagonist
 - Buspirone (14–45 mg/day) - 5HT1A partial agonism
 - Yohimbine (5–10mg/day) - α -2 adrenergic antagonism
 - Amantadine (100–400 mg/day) - Dopamine agonist
 - Bupropion (150-300mg/day) - NET reuptake inhibitor, DA reuptake inhibitor. Has good evidence for its usefulness. ^[42,43]
 - Mirtazapine (7.5 – 45 mg/day) - Antagonist on 5-HT2 and 5-HT3 receptors Presynaptic α 2-receptor blockade. Mirtazapine significantly improved sexual dysfunction in open label studies. ^[44]
- **Add- on agents for erectile dysfunction ^[11]**
 - PD-5 inhibitors – sildenafil, vardenafil, and tadalafil. These are well tolerated and effective for reducing erectile dysfunction associated with antidepressants. ^[45-49] However, as their use requires prior planning, spontaneity may be hampered.
- Aripiprazole, (2-20 mg/day), with its partial dopaminergic agonism and 5HT2 receptor antagonism has been shown to improve desire and sexual satisfaction in patients with depression; in women, the improvement in sexual interest and satisfaction was independent of the improvement in depressive symptoms. ^[50]
- Local application of testosterone gel/cream can improve sexual functioning (especially ejaculatory function) in depressed males with low or low-normal testosterone levels on serotonergic antidepressants ^[51].

Low risk	Agomelatine, Bupropion, Nefazodone, Selegiline, Trazodone, Vilazodone, Vortioxetine
Intermediate risk	Desvenlafaxine, Duloxetine, Escitalopram, Fluvoxamine, Mirtazapine, Moclobemide, Reboxetine
High risk	Amitriptyline, Citalopram, Clomipramine, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline, Venlafaxine

Table 4 : Risk stratification of TEDS related to Antidepressants^[1]

Clinical Recommendations^[11]

Initiate treatment with drugs that have low propensity for causing sexual dysfunction in sexually active patients. Agomelatine, mirtazapine, and bupropion cause have better sexual side effect profile. If some serotonergic action is preferable, desvenlafaxine and vortioxetine at lower doses can be used.

If TEDS develops, the following are the options-^[11]

A: Recommended (good evidence that the measure is effective, and the benefits far outweigh the harms).

B: Recommended (at least moderate evidence that the measure is effective, and the benefits outweigh the harms).

C: Neither recommended nor inadvisable (at least moderate evidence that the measure is effective; however, the level of benefit is very similar to the level of harm and a general recommendation cannot be justified)

Low sexual desire-

- Switching to agomelatine – Evidence level A
- Switching to non-serotonergic Antidepressant (bupropion, mirtazapine) - Evidence level B
- Adding bupropion - Evidence level B
- Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- Reducing the dose of the offending medication; adding aripiprazole - evidence level C

Orgasm retardation –

- Switching to agomelatine – Evidence level A
- Switching to non-serotonergic antidepressant or fluvoxamine- Evidence level B
- Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- Reducing the dose of the offending medication - Evidence level C

Anorgasmia –

- Switching to agomelatine – Evidence level A
- Switching to non-serotonergic antidepressant or fluvoxamine- Evidence level B
- Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- Reducing the dose of the offending medication - Evidence level C

Erectile dysfunction-

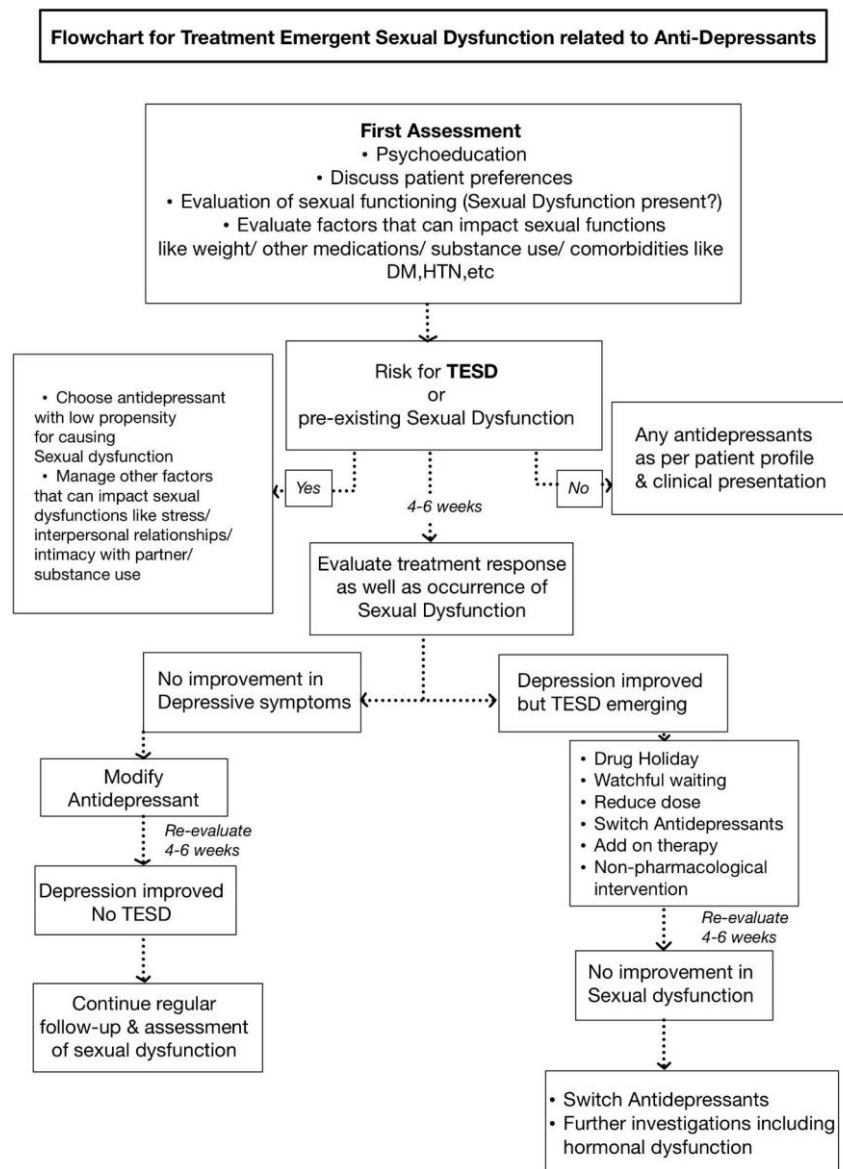
- Switching to agomelatine – Evidence level A
- Switching to non-serotonergic antidepressant - Evidence level B
- Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- Add PDE5 inhibitors - Evidence level B

Scarce vaginal lubrication-

- Switching to agomelatine – Evidence level A
- Switching to non-serotonergic antidepressant - Evidence level B

- Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- Reducing the dose of the offending medication; vaginal lubricants - Evidence level C

Figure 3: Flowchart for management of TESD related to antidepressants



Management Strategies for Antipsychotic related TEDS

Box 5

General Principles-

- Comprehensive evaluation to rule out psychiatric or physical comorbidities which may contribute to sexual dysfunction
- To check if the patient is on any other medication or takes any substance which can cause sexual dysfunction.
- If there are symptoms suggestive of hyperprolactinemia, assessment should include measurement of serum prolactin levels.
- Modification of risk factors where feasible (healthy lifestyle, weight management, stress management, treatment of any substance addiction and smoking cessation, physical exercise, relaxation exercises, maintaining good glycemic control in diabetics, treatment of dyslipidemia and hypertension).
- Remaining vigilant about the risk of TEDS and ensuring that sexual function is assessed in every follow-up. It is important to remember that patient may not spontaneously complain about sexual dysfunction and it is necessary to ask clear questions.

Pharmacological interventions^[14]

Waiting for Spontaneous remission of TEDS – If the sexual dysfunction is consequent to the severity of psychosis, treatment of the disorder can hypothetically improve sexual functioning. Very few studies have reported spontaneous improvement in antipsychotic related TEDS over time and this strategy is not recommended as sexual dysfunction may persist, leading to treatment non adherence.

Dose reduction^[14]

Reducing the dose of the antipsychotic to the minimum effective dose can be beneficial in improving SD in some cases. However, the correlation between antipsychotic dosage and sexual dysfunction is not absolutely certain and there can be a lot of individual variability. Reducing the dosage can precipitate relapse of illness and this strategy can only be attempted who have been stable for some time. The treatment regimen should be simplified and other drugs like sedatives and anticholinergics which can influence sexual functioning should be taken into account when considering TEDS. The treatment plan has to be customized for each patient, taking into account the risk-benefit ratio and patient and partner preferences.

Switching^[14]

If the patient has severe SD and reducing the dosage is not feasible, one strategy is to switch to an antipsychotic with less propensity for causing SD.

The most robust evidence for switching is for aripiprazole. Multiple studies have demonstrated that aripiprazole at around dose range of 15 mg/day improves SD (desire, arousal and orgasm) and switch to aripiprazole from other antipsychotics like risperidone, quetiapine, amisulpride, olanzapine, clozapine, paliperidone and typical antipsychotics reduces prolactin levels ^[52-55]. Among the newer drugs, Brexpiprazole, a metabolite of aripiprazole has shown promising results in reducing prolactin levels in clinical trials, but further research is needed.

Olanzapine, which acts by strong 5HT_{2A} antagonism and moderate D₂ and 5HT_{2C} antagonism, causes hyperprolactinemia at doses above 15 mg/day. At lower doses, it causes less sexual dysfunction compared to risperidone and haloperidol. ^[56-58]

Dopamine agonists can be used to manage the hyperprolactinemia caused by antipsychotics. Cabergoline (0.125-0.250mg/week) ^[59] and bromocriptine (2.5-10mg/day) ^[60] when used prudently has been shown to reverse antipsychotic induced hyperprolactinemia and improve sexual functioning. However, dopaminergic drugs need to be administered with caution as they can exacerbate psychosis. Few small studies have reported benefits after switching to ziprasidone and lurasidone but the quality of evidence is poor.

Adjunctive treatments

When dose reduction or switching is not feasible, one option is to add an adjunctive medication to improve the SD. Multiple randomized studies have shown that adding aripiprazole to the existing antipsychotic can improve SD as well as reduce prolactin level, probably via its partial dopaminergic agonism. It is well tolerated as an add-on drug and the dose can be tailored as per the patient's requirement. ^[53-55]

Phosphodiesterase-5 (PDE-5) inhibitors can be used to manage antipsychotic induced erectile dysfunction in males. PDE-5 inhibitors act by enhancing penile vasodilation and targeting the nitric oxide inhibition caused by some antipsychotics. Small randomized control trials have reported good results with sildenafil, tadalafil and vardenafil. ^[61-63]

Box 6

Non-Pharmacological interventions

- Psychoeducation of patient and partner – Patients with psychosis can have widely variable clinical presentation, sexual functioning and treatment response and in each case, the approach has to be customized. In an acutely psychotic patient, stabilization of psychotic may take precedence over assessment of sexual functioning. Once TESD occurs, it may not always be possible to fully restore previous levels of sexual functioning. The treatment approach should try to bring about an acceptable balance between treatment of psychiatric symptoms and sexual functioning, taking into account patient preferences. Psychoeducation about possible adverse sexual side effects of antipsychotics, addressing concerns about reversibility and impact on relationship will be reassuring for the patient and partner.
- Clarify myths/misconceptions about sexuality
- Lifestyle modification, weight management, exercise, focusing on partner intimacy and interpersonal relationships, stress management.
- Specific therapies like dual sex therapy, CBT (to address maladaptive beliefs), mindfulness - based exercises can be used.

Clinical Recommendations ^[14]

Initiate treatment with antipsychotics that have less propensity for causing SD. Aripiprazole, quetiapine, ziprasidone, and olanzapine <15mg/day can be chosen. Avoid risperidone, paliperidone, amisulpride, and typical antipsychotics as first choice if sexual dysfunction is a concern.

If TESD develops, the following are the options ^[14]

A: Recommended (good evidence that the measure is effective, and the benefits far outweigh the harms).

B: Recommended (at least moderate evidence that the measure is effective, and the benefits outweigh the harms).

C: Neither recommended nor inadvisable (at least moderate evidence that the measure is effective; however, the level of benefit is very similar to the level of harm and a general recommendation cannot be justified)

Low sexual desire-

- Switching to aripiprazole – Evidence level A

- Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level B
- Adding aripiprazole - Evidence level B
- Switching to olanzapine <15mg/day - Evidence level B
- Reducing the dose of the offending medication - Evidence level C

Orgasm retardation –

- Switching to aripiprazole – Evidence level A
- Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level B
- Adding aripiprazole - Evidence level B
- Switching to olanzapine <15mg/day - Evidence level B
- Reducing the dose of the offending medication - Evidence level C

Anorgasmia –

- Switching to aripiprazole – Evidence level A
- Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level B
- Adding aripiprazole - Evidence level B
- Switching to olanzapine <15mg/day - Evidence level B
- Reducing the dose of the offending medication - Evidence level C

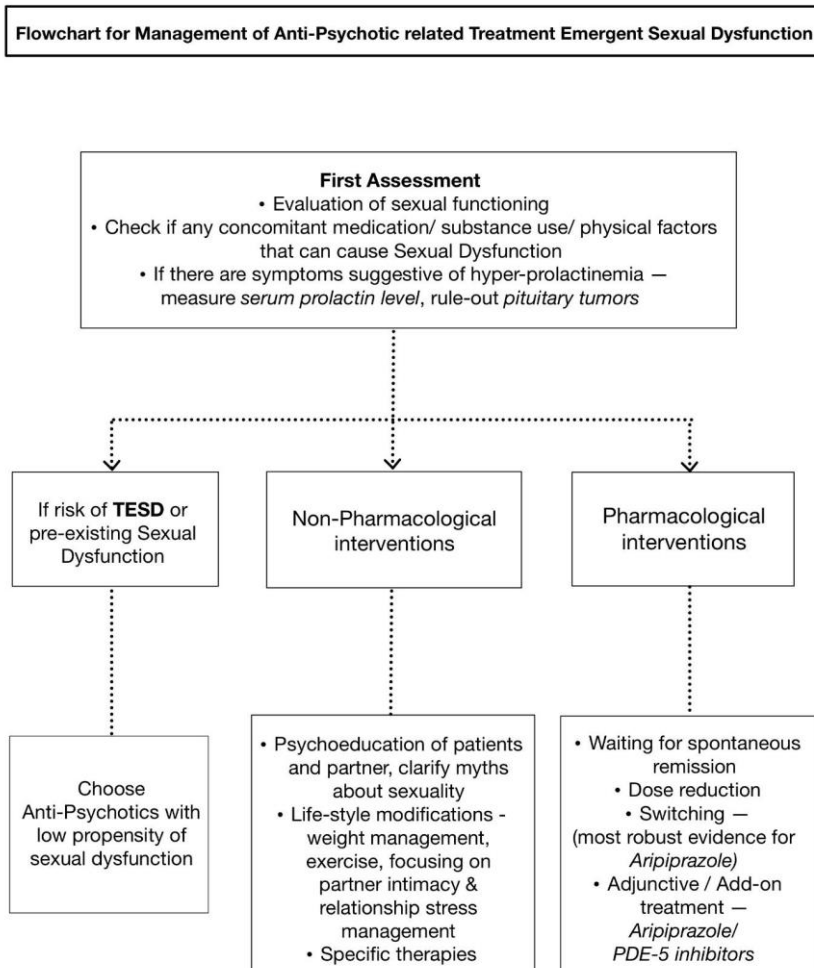
Erectile dysfunction-

- Switching to aripiprazole – Evidence level A
- Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level B
- Adding PDE5 inhibitors - Evidence level B
- Switching to olanzapine <15mg/day - Evidence level B
- Reducing the dose of the offending medication - Evidence level C

Scarce vaginal lubrication-

- Switching to aripiprazole – Evidence level A
- Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level B
- Using vaginal lubricants - Evidence level B
- Switching to olanzapine <15mg/day - Evidence level B
- Reducing the dose of the offending medication - Evidence level C

Figure 4: Flowchart for management of TESD related to antipsychotics



Management of TESD related to mood stabilizers

Robust literature on management of TESD associated with mood stabilizers is lacking. Some of the general strategies for management of TESD may be used like switching to drugs with low risk for TESD like lamotrigine, using the minimum effective dose and addition of adjunctive medications. Switching to lamotrigine as well as addition of lamotrigine to carbamazepine or valproate has shown improvement in sexual functioning.^[64,65] Switching to lamotrigine or oxcarbazepine from valproate or carbamazepine has also shown benefit in sexual functioning.^[19] In males on lithium, erectile dysfunction improved on

addition of aspirin in a small RCT. ^[66] Literature on the adjunctive use of PDE5 inhibitors in patients on mood stabilizers is lacking.

Treatment emergent sexual dysfunction associated with non- psychotropic drugs

Treatment emergent sexual dysfunction is a common but underrecognized adverse effect of many non-psychotropic medications used for the treatment of common medical conditions. In particular, erectile dysfunction has been reported extensively with many classes of prescription drugs. Recognizing the risk of drug induced sexual dysfunction and their negative effect on treatment compliance will help the clinician to tailor the treatment as per the patient's needs and preferences. The table provided below gives an overview of the various classes of non- psychotropic drugs associated with sexual dysfunction.

Class of drugs	Higher risk	Lower risk/neutral	Comments
Antihypertensives ^[67-70]	- Non- selective beta blockers (Propranolol, Nadolol, Timolol) - Older beta blockers (Metoprolol, Atenolol) - Centrally acting agents (α-Methyldopa, Clonidine, Reserpine) - Thiazide diuretics (especially hydrochlorthiazide)	- Angiotensin Converting Enzyme (ACE) inhibitors (Enalapril, Ramipril, Perindopril) - Angiotensin II receptor blockers (ARBs) (Losartan, Telmisartan, Valsartan) - Calcium channel blockers (Amlodipine, Diltiazem) - Alpha-blockers - Newer beta blockers (Nebivolol)	- ARBs and Nebivolol have the best evidence for preserving/ improving erectile function. - Nebivolol may increase peripheral nitric oxide availability and may improve erectile function. - There is inconclusive evidence regarding negative impact of thiazides in recent literature.
Drugs used for treatment of Congestive Cardiac failure/ ischemic heart disease/arrhythmia ^[67, 71-73]	- Loop diuretics - Thiazide diuretics - Spironolactone - Digoxin - Non- selective and older beta blockers	- ACE inhibitors - ARBs - Nebivolol - Mineralocorticoid receptor antagonist (Eplerenone)	Eplerenone has substantially less endocrine toxicity
Drugs used for the treatment of diabetes mellitus ^[74, 75]	Sulfonyl ureas (Inconclusive evidence)	- Metformin - Dipeptidyl peptidase 4 (DPP-4) inhibitors (Sitagliptin,	- Optimum glycaemic control itself is associated with better sexual function. - GLP-1 agonists and SGLT-2 inhibitors may improve

		Vildagliptin, Linagliptin) • Glucagon like peptide 1 receptor agonists (GLP-1-RA) (Semaglutide, Liraglutide) • Sodium-glucose co-transporter2 inhibitors (SGLT2i) (Dapagliflozin, Empagliflozin, Canagliflozin, Remogliflozin) • Thiazolidinediones	sexual functioning through weight loss and cardiometabolic benefits.
Lipid lowering drugs ^[76-78]		• Statins • Fibrates	• Inconclusive evidence. • Earlier studies suggested that both statins and fibrates can cause ED. • Recent studies indicate improvement of sexual function with statins by improving endothelial nitric oxide synthase activity and increasing nitric oxide bioavailability while subgroup analysis reported increased ED risk with lipophilic statins compared to hydrophilic rosuvastatin.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ^[72, 79]		• Regular NSAID use especially Aspirin linked to ED	Inconclusive evidence
Gonadotropin-releasing hormone (GnRH) analogues ^[80-82]	GnRH agonists GnRH antagonists		Both GnRH agonists & antagonists reduce levels of luteinizing hormone and follicle-stimulating hormones, which in turn lowers testosterone to castrate levels. Used to reduce gonadotropin levels in central precocious puberty

Contraceptive drugs ^[83, 84]		Hormonal contraceptives linked to low desire and reduced lubrication in few studies	- For low desire switching from hormonal to non-hormonal, from oral to non-oral or from estrogen-containing to no-estrogen-containing forms of contraception. - In case of contraception-related reduced lubrication or Vulvo vaginal atrophy, switch from hormonal to non-hormonal or from oral to non-oral forms of contraception; in addition, a switch to Combined oral contraceptives with higher ethinylestradiol doses may be beneficial
H ₂ Antagonist Antacids ^[85, 86]	Cimetidine	Ranitidine	Cimetidine causes direct androgen receptor blockade, testosterone synthesis inhibition and can cause gynaecomastia
Steroids ^[87-89]	Anabolic androgenic steroids (AAS) Glucocorticoids		AAS suppresses Hypothalamo-pituitary-gonadal axis, causing hypogonadism, reduced libido, erectile dysfunction, gynecomastia, and impaired spermatogenesis Glucocorticoid treatment can reduce sexual desire and cause erectile dysfunction
5 alpha reductase inhibitors ^[90]	Finasteride Dutasteride		Both finasteride and dutasteride can cause impotence, reduced libido, and ejaculation disturbances. Post-finasteride Syndrome (PFS), describes a host of sexual, physical, and neurologic symptoms associated with 5-ARIs that can persist after stopping the drug
Antiretroviral therapy ^[91-94]		Protease inhibitors Dolutegravir (HIV 1 integrase inhibitor)	Mixed evidence Association between ED and protease inhibitors can be caused by induced neuropathy (indinavir), effects on sex hormone metabolism

			(ritonavir) or indirectly due to concomitant medications. Dolutegravir can cause ED and reduced desire in males.
Antifungal agents [95-96]	Azole antifungals		Azole antifungals especially ketoconazole can lead to gynecomastia, decreased libido, oligospermia, azoospermia, impotence
Immunosuppressive drugs ^[97]	Rapamycin inhibitors (Sirolimus Everolimus)		Rapamycin inhibitors (TOR I) reduces testosterone levels and impairs spermatogenesis
Opioid analgesics ^[98]	Oxycodone		Oxycodone is a mu opioid receptor agonist that inhibits ascending pain pathways and can cause ED. Opioids can disrupt the hypothalamic-pituitary gonadal axis by binding to m receptors in the hypothalamus leading to negative feedback, decreased gonadotropins and secondary hypogonadism.

Table 5 Non psychotropic drugs associated with sexual dysfunction

Strategies to manage sexual dysfunction associated with non-psychotropic drugs

- Psychoeducation- Sexual dysfunction can be multifactorial and arise due to the disease process itself or as a consequence of medication. Patients with chronic illnesses may often be unaware that sexual dysfunction has developed as a consequence of their treatment. On the other hand, others may blame their drugs for sexual problems which have occurred due to psychosocial factors. In each case, the sexual functioning of the patient has to be considered when planning the treatment.
- Switching to an alternative drug with less potential for causing sexual dysfunction
- In men, phosphodiesterase type 5 inhibitor in anticipation of intercourse (contraindicated if the patient is on nitrates).

Comparison of various phosphodiesterase 5 inhibitors for erectile dysfunction^[99]

Drug name	Sildenafil	Tadalafil	Vardenafil	Avanafil
Timing of dose	60 minutes prior	At least 30 minutes prior	25-60 minutes prior	15-30 minutes prior

Max plasma concentration	30-120 minutes Median 60 minutes	30-360 minutes Median 120 minutes	30-120 minutes Median 60 minutes	30-120 minutes Median 30-45 minutes
Half life	3-5 hours	17.5 hours (healthy men) 21.6 hours (elderly men)	4-5 hours	3-5 hours
Daily dosing	No	Yes	No	No
Available doses in mg	25, 50, 100	2.5, 5, 10, 20	2.5, 5, 10, 20	50, 100, 200
Recommended starting doses in mg/day	50	10	10	100
Maximum dose in mg/day	100	20	20	200
Affected by fatty meal	Yes	No	Yes	Yes
Side effects	Rhinitis, dyspepsia, headache, flushing, vision changes	Headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb	Headache, flushing, rhinitis, dyspepsia	Headache, flushing, nasopharyngitis, nasal congestion
Contraindications	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet

Conclusion

Treatment emergent sexual dysfunction is a clinically relevant and often unrecognized adverse effect of psychotropic as well as non-psychotropic medications. It can have a significant negative impact on quality of life, interpersonal relationships, self-esteem, and most alarmingly, treatment adherence. Patients are often reluctant to disclose sexual problems spontaneously. Clinicians need to be cognizant of these concerns and evaluate sexual functioning with sensitivity by using validated tools. Sexual functioning assessment should be part of the routine clinical evaluation throughout the course of the treatment. Assessment where TESD is suspected should be comprehensive and take into account the baseline sexual functioning, physical examination, temporal relationship with the offending drug, dose and duration of exposure, concomitant medications, substance use, medical comorbidities and relationship or psychosocial factors. Management should follow a patient-centered, risk-benefit approach, taking into account the patient/partner preferences. If possible, selection of agents with a lower propensity for sexual adverse effects should be considered in patients for whom sexual functioning is an important treatment priority. Once dysfunction develops, management may include

modification of contributing factors, dose optimization, switching to an alternative medication with a more favourable sexual adverse-effect profile, or addition of an appropriate symptomatic treatment. Such decisions should take into account the severity and persistence of sexual dysfunction, the response to the primary treatment, relapse risk, comorbidities, drug interactions and patient preferences. Non pharmacological interventions like psychoeducation, modification of risk factors where possible and specific psychotherapies if indicated are important. To reiterate, sexual side effects should be taken into account when considering the pros and cons of different treatment modalities. Enquiring proactively, assessing systematically, identifying reversible contributors, discussing options openly with the patient, and individualizing treatment according to the balance between psychiatric/medical benefit and sexual adverse effects remains integral to good clinical practice.

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Clinical Practice Guidelines on Treatment Emergent Sexual Dysfunctions

EXECUTIVE SUMMARY

Problem statement

Treatment emergent sexual dysfunction (TESD) is one of the most unrecognized adverse effects of psychotropic treatment and non-psychotropic treatment. It affects 25-80% of patients on antidepressants and 16-60% of patients on antipsychotics. Many non-psychotropic medications used for the treatment of common medical conditions have also been implicated in the occurrence of TESD. It is one of the chief causes of medication non-adherence and treatment discontinuation across all psychiatric diagnoses.

Pathophysiology

TESD arises from disturbance of the dopaminergic, serotonergic, adrenergic, cholinergic and hormonal axes regulating the sexual response cycle. SSRIs and SNRIs primarily cause TESD by 5HT_{2A/2C} receptor overstimulation and resulting dopamine suppression. Antipsychotics act via tuberoinfundibular D₂ blocking, leading to hyperprolactinemia and resulting hypogonadism. Mood stabilizers like carbamazepine act by enzyme induction, thereby reducing sex hormone bioavailability, while sodium valproate is associated with Polycystic Ovarian Syndrome (PCOS). Understanding these mechanisms is imperative to rational agent selection and targeted management of adverse sexual side effects.

Assessment

ASEX is the recommended minimum screening tool at every clinical contact. The PRSexDQ specifically attributes dysfunction to medications. The IIEF and FSFI are gold-standard domain specific assessment for male and female patients respectively. Serum prolactin, sex hormone panel (testosterone, LH, FSH, estradiol) and thyroid function should be a necessary part of baseline and monitoring investigations for all antipsychotic treated patients.

Management of antidepressant related sexual dysfunction

Most cases of TESD do not resolve spontaneously even after 6 months, and are often underreported. Hence routine screening is essential. Non-drug measures like psychoeducation, lifestyle changes, specific techniques like Kegel exercises, sensate focus, start-stop/ squeeze techniques for premature ejaculation, sex therapy or CBT can be tried. Drug strategies include waiting for tolerance in mild cases, reducing the dose, switching to a lower risk antidepressant (e.g., bupropion, agomelatine, mirtazapine, vortioxetine), or augment with agents like bupropion, buspirone, or PDE-5 inhibitors.

Management of antipsychotic associated sexual dysfunction

General principles and non-pharmacological treatment are similar to that of antidepressant induced sexual dysfunction. Ruling out hyperprolactinemia is primary, apart from excluding co-offending agents or specific comorbidities causing sexual dysfunction. Waiting for spontaneous remission is not advisable. Reducing the dose of antipsychotic is not always a feasible option, due to nonlinear relationship between dosage and sexual side effects. Moreover, reducing dose of antipsychotics can cause relapse of psychotic symptoms.

For all antipsychotic associated sexual dysfunction, the best recommended practice is to switch to aripiprazole. The second level of evidence stands for adding aripiprazole to the existing treatment regime, or using olanzapine <15 mg/ day, or quetiapine/ ziprasidone. For erectile dysfunction, PDE5 inhibitor addition and for vaginal dryness, use of vaginal lubricants have second level of evidence.

Management of mood stabilizer associated sexual dysfunction

Robust literature is lacking. Most evidence is for switching or adding lamotrigine to existing therapy. Addition of aspirin was shown to be beneficial in lithium TESD in a small RCT.

TESD associated with non-psychotropic medications

Cardiovascular drugs, (especially non selective and older generation beta blockers, thiazide diuretics and loop diuretics, digoxin and centrally acting agents), antidiabetic and lipid lowering agents, anticancer medications, opioid analgesics, contraceptives, Gonadotropin-releasing hormone (GnRH)

52 analogues, antiretroviral therapy, steroids, 5 alpha reductase inhibitors, anti fungals and
53 immunosuppressive drugs have all been implicated in the development of TESD. Management
54 strategies may include modification of contributing factors, dose optimization, switching to an
55 alternative medication with a more favorable sexual adverse-effect profile, or addition of an appropriate
56 symptomatic treatment.

57 To sum it up, management is stepwise and tailored to patient needs- starting with psychoeducation and
58 lifestyle measures, escalating to dose adjustment or switching, and implementing augmentation
59 strategies for patients where switching is not feasible. The whole process should follow a collaborative
60 approach for better long-term outcome.

61
62
63

64 **Introduction**

65 Sexual health is a basic domain of human well-being, and inseparable from overall health and quality
66 of life. Psychotropic medications, though transformative in reducing the overall burden of mental
67 illness, are associated with a significant iatrogenic challenge: Treatment emergent sexual dysfunction
68 (TESD). The term encompasses a wide spectrum of medication induced impairments spread across the
69 phases of sexual cycle, including decreased libido (hypoactive sexual desire disorder), impaired arousal
70 (erectile dysfunction in men; reduced lubrication and genital engorgement in women), delayed or absent
71 orgasm (anorgasmia, delayed ejaculation), and ejaculatory dysfunction.

72 TESD is a substantial and common burden in psychiatric practice. The fifth International Consultation
73 on Sexual Medicine (ICSM, 2024) reported that it affects 25-80% of patients on antidepressants and
74 16-60% of those on antipsychotics.^[1]

75 The clinical consequences of TESD extend far beyond patient distress. They are one of the most
76 common reasons for medication non-adherence. As compared to other side effects associated with
77 psychotropics like weight gain, sedation and dry mouth, sexual side effects have a tendency to persist.
78 A review by Montejo et al^[2] reaffirmed that TESD tends to persist over time and are underrecognized
79 by clinicians and less investigated in clinical trials. This is due to a mutual reluctance to discuss sexual
80 functions on the part of the patients and the clinicians.

81 **Pathophysiology**

82 Masters and Johnson developed the four-phase model of the sexual cycle- excitement, plateau (where
83 the physiological changes of excitement are continued and intensified), orgasm, and physiological
84 resolution. Helen Singer Kaplan proposed the three-phase model, where desire is the first phase
85 followed by excitement and orgasm. Desire incorporates the psychological motivational factors that are
86 central to initiation of physiological responses, since problems of desire (low libido) are different from
87 problems of physiological arousal. The phase of resolution was not described explicitly in Kaplan's
88 model for the purpose of clinical simplicity.

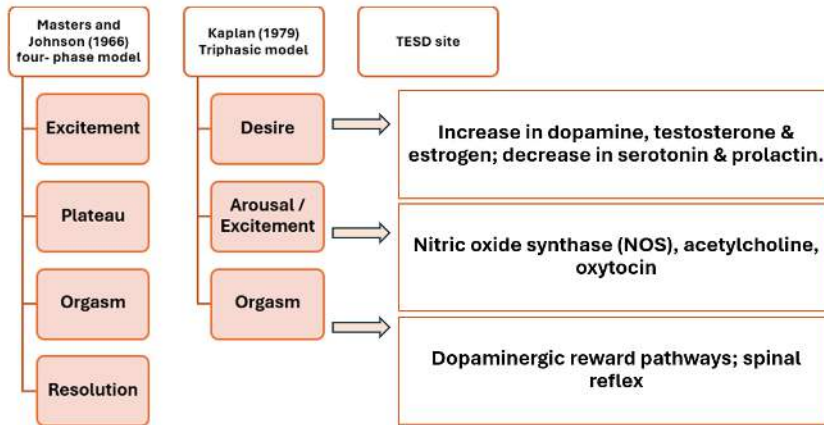


Figure 1: Phases of the human sexual response cycle ^[3,4]

Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin Noradrenaline Reuptake Inhibitors (SNRI) cause excess stimulation of the 5HT_{2A} and 2C receptors in the limbic system and hypothalamus, which leads to a tonic inhibition of dopamine release (damping sexual motivation and reward) and additionally inhibit Nitric Oxide Synthase (NOS) in the genital tissue, decreasing vasodilatory arousal responses. These side effects may be dose dependent and show some response to reduction in dose. ^[5,6]

5HT_{2C} activation also causes elevation of prolactin, leading to suppression of libido. Peripherally, delayed ejaculatory reflex at the level of sacral spinal cord may lead to delayed or absent orgasm. ^[7]

Tricyclic antidepressants (TCA) cause sexual dysfunction through diverse pathways: Serotonergic mechanism, which is shared with SSRIs, anticholinergic action (leading to genital vasoconstriction and impaired genital lubrication), antihistaminergic activity (causing sedation) and alpha blockade (damping erection and ejaculation). Clomipramine particularly has very high rates of TESSD. Genetic susceptibility studies show that a higher SERT affinity leads to a higher risk of TESSD, while a higher 5HT_{2C} affinity leads to a lower risk of TESSD. ^[8]

CYP2C19 metabolizer phenotypes, 5HTR_{2A}, SLC6A4, glutamatergic receptor polymorphisms also influence TESSD susceptibility. ^[9,10]

Antidepressants with low propensity for TESSD include bupropion, mirtazapine, agomelatine and vortioxetine. Bupropion may enhance sexual function in addition to effects on smoking cessation. ^[11]

Drug	Prevalence of TESSD	Phase of sexual response
Moclobemide	0.22%	Desire, orgasm, arousal
Agomelatine	0.25%	Desire, orgasm
Bupropion	0.75%	Desire, orgasm, arousal
Mirtazapine	2.32%	Desire, orgasm, arousal
Fluvoxamine	3.27%	Desire, orgasm, arousal
Escitalopram	3.44%	Desire, orgasm, arousal
Duloxetine	4.36%	Desire, arousal

Imipramine	7.24%	Desire, orgasm, arousal
Fluoxetine	15.59%	Desire, orgasm, arousal
Paroxetine	16.68%	Desire, orgasm, arousal
Citalopram	20.27%	Desire, orgasm, arousal
Venlafaxine	24.82%	Desire, orgasm, arousal
Sertraline	27.43%	Desire, orgasm, arousal

Table 1: Phases of sexual response cycle affected by antidepressants ^[12]

Antipsychotics

Mechanism of action of antipsychotic induced SD^[13]

- Dopamine receptor antagonism leads to inhibition of motivation and reward and decreased desire. First-generation antipsychotics (haloperidol, pimozide, trifluoperazine) and risperidone can blunt sexual desire, inhibit reward and cause anorgasmia or erectile dysfunction independent of prolactin by direct dopaminergic suppression in the mesolimbic pathway. ^[13]
- Dopamine D2 receptor antagonism (tubero-infundibular pathway) leads to hyperprolactinemia and thereby causes decreased desire, impaired arousal, impaired orgasm.
- Partial D2 agonists like aripiprazole, brexpiprazole and cariprazine have favorable sexual side effects profile. ^[14]
- Histamine receptor antagonism causes sedation and impairs arousal.
- Cholinergic receptor antagonism leads to reduced peripheral vasodilation, thereby causing erectile dysfunction. The anticholinergic effects of first-generation antipsychotics like chlorpromazine and add-on drugs like trihexyphenidyl are noted for causing erectile dysfunction, decreased genital sensations, as well as delayed or retrograde ejaculation.
- α -adrenergic antagonism leads to reduced peripheral vasodilation, causing priapism, decreased erection/lubrication, abnormal ejaculation.
- Serotonergic effects mediated by increased stimulation of 5HT_{2A/2C} receptors by second generation antipsychotics like risperidone or quetiapine can lead to decrease in libido, as well as anorgasmia.

Prolactin and antipsychotics

- Prolactin raising antipsychotics – Amisulpride, haloperidol, paliperidone, risperidone, other typical antipsychotics
- Prolactin sparing antipsychotics – Aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone

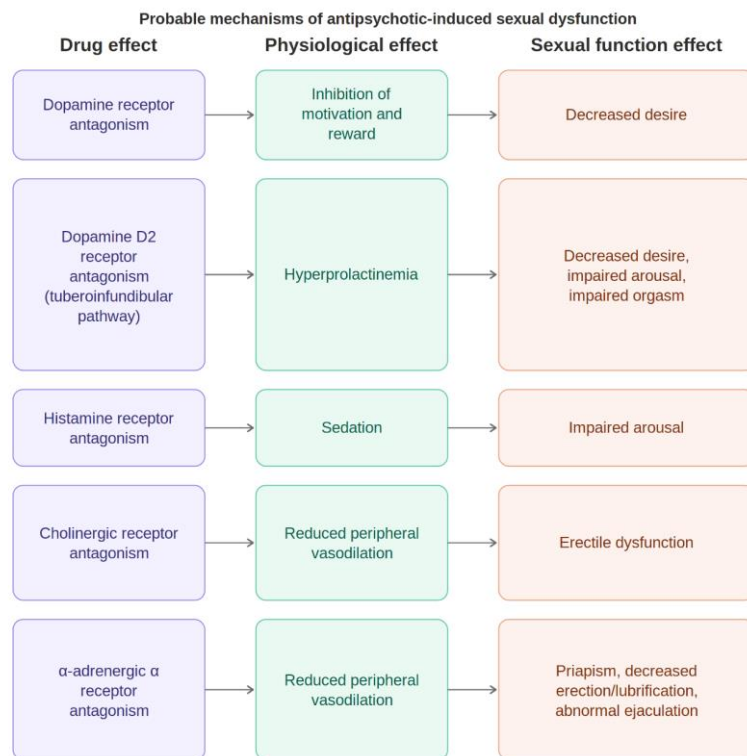


Figure 2. Summary of probable mechanisms of antipsychotic induced sexual dysfunction

Mood stabilizers

Lithium- It has been shown to cause suppression of sexual desire, hypoarousal symptoms, erectile dysfunction and orgasmic dysfunctions. Though the exact mechanisms remain unclear, it has been postulated that lithium can cause sexual dysfunction by its effects on neuroendocrine signaling, neurotransmitter modulation, and hormonal balance, which can interfere with normal erectile physiology. Additionally, it causes thyroid dysfunction, which itself may hamper sexual function.^[2]

Carbamazepine is an enzyme inducer, and may increase hepatic metabolism of sex hormones, lowering their bioavailability. Valproate is associated with increased risk of Polycystic Ovary Syndrome (PCOS) in women, which alters the hormonal environment required for optimal female sexual function.^[15]

Lamotrigine is enzyme neutral in its kinetics and causes least TESD.^[15] Gabapentin and topiramate can cause difficulties in orgasmic in both men and women, and has also been shown to be associated with reduced libido in women.^[16-18]

Benzodiazepines

The literature on sexual side effect of benzodiazepines is limited, and insufficient to draw any definitive conclusions.^[19]

Some studies do show evidence for sexual dysfunction associated with benzodiazepines, but the evidence is conflicting.^[20]

The main postulated mechanism is GABAergic inhibition of central arousal and dopaminergic reward circuits. A 1992 study by Ghadirian and colleagues found that coadministration of benzodiazepines

158 with lithium was associated with substantially higher rates of sexual dysfunction (49%) compared with
159 lithium alone (14%). [21]

160 **Assessment**

161 **The basic outlines of assessment of TESD are given in Box 1 below:**

Box 1				
• Spontaneous reporting has low validity • Structured clinician-initiated interviews with validated instruments captures reliable information • Baseline sexual function assessment should be performed before starting any psychotropic, and should be repeated at follow up appointment • Assessment should inquire specifically into each phase of the sexual cycle (desire, arousal, orgasm, resolution) • Specific inquiry into patient’s subjective distress regarding sexual dysfunction. • Use of gender affirming, non-judgmental language preferably adapted to the patient’s cultural context. • Temporal relationship between medicine initiation and symptom onset to address causality.				

162
163 The salient features of tools used in the assessment of TESD are given in Table 2.

Instrument	Gender	Domains	Number of items	Comments
ASEX	Male & female	Drive, arousal, lubrication/ erection, orgasm, satisfaction	5	Brief, validated, wide usage. Cutoff ≥ 19 s/o Sexual dysfunction.
CSFQ-14	Male & female	Desire, arousal, orgasm	14	Gender specific scoring, sensitive to drug induced changes
PRSexDQ	Male & female	Desire, arousal/erection/lubrication, orgasm/ejaculation, global satisfaction	6	TESD specific, clinician administered
IIEF-15/IIEF-5	Male	Erectile function, orgasmic function, desire, satisfaction	15/5	Gold standard for male erectile dysfunction.
FSFI	Female	Desire, arousal, lubrication, orgasm, satisfaction, pain	19	Gold standard for female sexual dysfunction. Cutoff < 26.55 ; covers 6 domains

164 ASEX: Arizona Sexual Experience Scale; CSFQ: Changes in Sexual Functioning Questionnaire;
165 PRSexDQ: Psychotropic Related Sexual Dysfunction Questionnaire; IIEF: International Index of
166 Erectile Function; FSFI: Female Sexual Function Index

167 Table 2: Tools used in the assessment of TESD.

168 The ASEX is recommended as a universal first line screening tool for both male and female patients
169 due to its simplicity, validated cutoff scores, and sensitivity across different psychotropic drug types.

170 [22] The PRSexDQ was developed by Montejo and colleagues specifically for antidepressant and

antipsychotic associated sexual dysfunction.^[23] The IIEF and FSFI are gold standards for more detailed domain specific sexual dysfunction in male and female patients.^[24, 25] Biological assessments are mandatory in evaluation of TESD and include evaluation of serum prolactin (for antipsychotic associated sexual dysfunction). Sex hormone analysis (testosterone, Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH), estradiol), thyroid profile and cardiovascular risk factors are indicated based on specific case requirements. All of this may have causative or contributory role in TESD and direct management protocol. The basic outlines of what needs to be asked by the clinicians have been enumerated in Table 3:

Domain	Question	Comments
Baseline sexual function	How was your sexual function prior to starting medication?	Documenting baseline will avoid confusion between TESD and preexisting sexual disorder
Desire	Have you noticed any change in your desire after starting/ adjusting this medication?	Desire, arousal and orgasm can be affected independently,
Arousal	Any difficulty in erections/ vaginal lubrication after starting/adjusting this medication?	Ask both about physiological and subjective arousal
Orgasm/ ejaculation	Have you noticed any delay/ difficulty to reach orgasm/ ejaculate?	Sensitive marker for SSRI/SNRI related TESD.
Satisfaction/ distress	How satisfied are you with your conjugal life, and how much does this problem bother you?	Distress warrants intervention, not just presence of mild symptoms.
Follow-up assessment	Re-administer a validated screening tool (ASEX, PRSexDQ) rather than reliance on patient self-report.	Use the same tool at each follow up visit for better comparability.

Table 3: Practical tips for clinicians: What to ask? ^[11, 22,23]

Management Strategies
Management Strategies for Treatment Emergent Sexual Dysfunction (TESD)

- For management of TESD, it is recommended that ^[1]-
- Practitioners should be aware of the risk of TESD and the interplay of various psychosocial factors, illness related factors and other medical or physical causes that can influence it.
 - Clinicians should remain vigilant and consistently assess for treatment emergent sexual dysfunction related to particular psychotropic agents throughout the entire course of treatment.

General Principles

Box 2

Prevent TESD in vulnerable population – use agents with low probability of incidence of SD

Routine assessment in clinical practice for emergence of TESD

Intervene once TESD occurs and is a concern for patient/partner

Box 3

Non- Pharmacological interventions

- Psychoeducation/sex education - Psychoeducation about possible adverse sexual side effects when initiating psychotropics as well as the potential sexual dysfunction associated with the disease process itself. If sexual side effects occur, address concerns about reversibility, impact on relationship and discuss management options which will be reassuring for the patient and partner.
- Clarify myths/misconceptions about sexuality
- General interventions to improve sexual health – healthy lifestyle, weight management, stress management, treatment of any substance addiction, focusing on partner intimacy and interpersonal relationships, physical exercise, relaxation exercises. Physical exercise has been shown to improve desire and sexual satisfaction in women on antidepressants ^[27].
- General techniques to improve sexual functioning like Kegels/ exercises and Sensate focus can be beneficial ^[26].
- For Premature ejaculation, start-stop technique and squeeze technique can be employed ^[26].

Specific psychotherapy ^[26]

- Dual sex therapy
- CBT
- Mindfulness based therapy

193 **Pharmacological interventions**

194 **Waiting for spontaneous remission** (adaptation/ tolerance) – This is a commonly used strategy by
 195 clinicians as some patients may report partial or complete improvement in treatment emergent sexual
 196 dysfunction within weeks to few months. However, clinicians need to be vigilant and assess sexual
 197 functioning in every follow-up as recent literature indicates that most patients (80%) do not report any
 198 significant improvement in sexual dysfunction after six months of treatment and unless specifically
 199 enquired undetected sexual dysfunction may persist and lead to nonadherence to treatment. ^[11] This
 200 strategy can be used in patients who have demonstrated treatment response to the chosen antidepressant,
 201 have mild sexual dysfunction with no significant distress or impairment (e.g. patients who are not
 202 sexually active) or in whom medications are not planned for long term. Patient preference is of
 203 paramount importance and any decision needs to be taken in a collaborative manner after
 204 comprehensive psychoeducation about the nature of sexual dysfunction, reversibility of side effects and
 205 options available to mitigate the side effect and pros and cons of the treatment.

206 **Reducing the dose or withdrawing antidepressant** – There is some evidence that suggests sexual
 207 dysfunction caused by SSRIs correlates with dose. ^[24] However, individual variations are common, with
 208 TSED occurring in some individuals at low doses. Reducing the dose of an antidepressant caused
 209 significant improvement in TSED in a prospective, multicentric study of 344 patients under treatment
 210 with SSRIs. ^[28] Abrupt dose reduction can precipitate relapse of depressive symptoms or discontinuation
 211 syndrome and this aspect should be considered. Patients on higher doses of medication who are in

212 remission can be considered for gradual dose reduction with careful monitoring of symptom severity,
213 keeping in mind not to titrate below the minimum effective dose. When dose reduction is being
214 considered, psychotherapy can be utilized as an adjunctive therapy. A recent concept talks about Post
215 SSRI Sexual Dysfunction (PSSD), where treatment emergent sexual dysfunction persists even after
216 discontinuation of SSRIs. It is proposed that for PSSD, the diagnostic criteria include prior treatment
217 with a serotonin reuptake inhibitor and an enduring change in somatic(tactile) or erogenous
218 (sexual)genital sensation after treatment stops. It is present for ≥ 3 months after stopping treatment and
219 may be accompanied by persistent reduction or loss in desire, erectile dysfunction or difficulty in
220 achieving orgasm.^[29]

221 Drug Holiday- This strategy is not usually recommended as it carries a high risk of relapse. Here
222 antidepressants are withheld or used at a lower dose few days before anticipated sexual activity. This
223 can only be used for drugs with a short half-life and in those patients in whom the depression is mild
224 and sexual dysfunction is debilitating.

225 **Switching to a drug with less propensity for causing sexual dysfunction** – This is a common strategy
226 employed by clinicians, the rationale being to switch to an effective and safe antidepressant with a
227 different mechanism of action which has lower risk of TESD. Switching from a SSRI to a non-
228 serotonergic or partially serotonergic class of medication can improve TESD.^[11] The commonly
229 preferred drugs for switching are-

230 **Non serotonergic drugs**^[11,26]

231 Bupropion- It acts by norepinephrine and dopamine transporter inhibition and is effective at a dosage
232 of 150-450mg/day. It is commonly used due to encouraging results from multiple studies. Increased
233 risk of seizures, exacerbation of anxiety and sleep disturbances can occur with bupropion and needs
234 vigilance. Bupropion may not be effective when used as the sole antidepressant and studies have looked
235 at combination of bupropion with SSRI to reduce TESD where switching is not feasible and it was
236 found that combining bupropion with SSRIs or venlafaxine improved the sexual functioning.^[30, 31]

237 Agomelatine – It has a noradrenergic and dopaminergic effect due to MT1 and MT2 melatonin receptor
238 agonism and 5HT2C receptor antagonism. The dose ranges from 25- 50 mg/day. Nausea and headache
239 are commonly reported adverse effects. RCTs comparing agomelatine to paroxetine^[32] and escitalopram
240^[33] have reported reduced occurrence of TESD with agomelatine while another study comparing
241 agomelatine to venlafaxine demonstrated comparable efficacy as antidepressant and reduced incidence
242 of TESD with agomelatine.

243 Mirtazapine - Mirtazapine is a noradrenergic and serotonergic dual-action AD which acts by
244 stimulation of 5HT1 postsynaptic receptors and blockade of 5HT2 and 5HT3 postsynaptic receptors
245 and $\alpha 2$ blockade. It is used at dose of 15- 45 mg/day. It causes prominent sedation and weight gain.
246 Improvement in TESD while maintaining antidepressant efficacy after switching to mirtazapine from
247 other ADs has been reported in observational studies.^[34,35]

248 **Partially serotonergic drugs**^[11,26]

249 In certain conditions switching to a non-serotonergic drug may not be efficacious and in these cases,
250 partially serotonergic medication may be considered. Desvenlafaxine works by norepinephrine and
251 serotonin transporter inhibition, is well tolerated and has good efficacy as antidepressant. TESD with
252 desvenlafaxine can occur at higher doses (above 100mg/day) but there is reduced likelihood at 50
253 mg/day.^[36] Observational studies have reported improvement in TESD after switching to
254 desvenlafaxine.^[37,38]

255 Vortioxetine has a multimodal mechanism of action and low serotonergic effect. In two controlled trials
256 where an SSRI was switched to either escitalopram or vortioxetine, significant improvement in sexual
257 functioning was demonstrated with vortioxetine and it had similar efficacy.^[39,40]

258 **Other Antidepressants**^[11,26]

259 Moclobemide- It is a reversible monoamine oxidase type A inhibitor used at a dosage of 300-600mg/day.
260 Switching to moclobemide has been shown to improve TESD and there are reports of stimulating effects
261
262

263 on sexual functioning with moclobemide use. ^[41] However, moclobemide requires a long washout
264 period when switching and its long-term utility is questionable.
265 Low incidence of TESD has been reported with reboxetine, trazodone, maprotiline and mianserin but
266 there is limited literature on the utility of switching to these agents.

267 **Augmentation/Add-on strategy**

268 Here, another agent is added to the existing treatment regimen, the rationale being to reduce the dose of
269 the offending drug and thereby bring about improvement in TESD.
270
271

Box 4

- **Add-on agents for improving anti-depressant induced anorgasmia ^[11]**
 - Cyproheptadine (4-8 mg/day) - 5HT antagonist
 - Buspirone (14–45 mg/day) - 5HT1A partial agonism
 - Yohimbine (5–10mg/day) - α -2 adrenergic antagonism
 - Amantadine (100–400 mg/day) -Dopamine agonist
 - Bupropion (150-300mg/day) - NET reuptake inhibitor, DA reuptake inhibitor. Has good evidence for its usefulness. ^[42,43]
 - Mirtazapine (7.5 – 45 mg/day) - Antagonist on 5-HT2 and 5-HT3 receptors Presynaptic α 2-receptor blockade. Mirtazapine significantly improved sexual dysfunction in open label studies. ^[44]
- **Add- on agents for erectile dysfunction ^[11]**
 - PD-5 inhibitors – sildenafil, vardenafil, and tadalafil. These are well tolerated and effective for reducing erectile dysfunction associated with antidepressants. ^[45-49] However, as their use requires prior planning, spontaneity may be hampered.
- Aripiprazole, (2-20 mg/day), with its partial dopaminergic agonism and 5HT2 receptor antagonism has been shown to improve desire and sexual satisfaction in patients with depression; in women, the improvement in sexual interest and satisfaction was independent of the improvement in depressive symptoms. ^[50]
- Local application of testosterone gel/cream can improve sexual functioning (especially ejaculatory function) in depressed males with low or low-normal testosterone levels on serotonergic antidepressants ^[51].

284
285

Low risk	Agomelatine, Bupropion, Nefazodone, Selegiline, Trazodone, Vilazodone, Vortioxetine
Intermediate risk	Desvenlafaxine, Duloxetine, Escitalopram, Fluvoxamine, Mirtazapine, Moclobemide, Reboxetine
High risk	Amitriptyline, Citalopram, Clomipramine, Fluoxetine, Imipramine, Nortriptyline, Paroxetine, Sertraline, Venlafaxine

286 **Table 4 : Risk stratification of TESD related to Antidepressants**^[1]

287 **Clinical Recommendations**^[11]

288 Initiate treatment with drugs that have low propensity for causing sexual dysfunction in sexually active
289 patients. Agomelatine, mirtazapine, and bupropion cause have better sexual side effect profile. If some
290 serotonergic action is preferable, desvenlafaxine and vortioxetine at lower doses can be used.

291 **If TESD develops, the following are the options-**^[11]

292 A: Recommended (good evidence that the measure is effective, and the benefits far outweigh the
293 harms).

294 B: Recommended (at least moderate evidence that the measure is effective, and the benefits outweigh
295 the harms).

296 C: Neither recommended nor inadvisable (at least moderate evidence that the measure is effective;
297 however, the level of benefit is very similar to the level of harm and a general recommendation cannot
298 be justified)

299 **Low sexual desire-**

- 300 ➤ Switching to agomelatine – Evidence level A
- 301 ➤ Switching to non-serotonergic Antidepressant (bupropion, mirtazapine) - Evidence level B
- 302 ➤ Adding bupropion - Evidence level B
- 303 ➤ Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- 304 ➤ Reducing the dose of the offending medication; adding aripiprazole - evidence level C

305 **Orgasm retardation –**

- 306 ➤ Switching to agomelatine – Evidence level A
- 307 ➤ Switching to non-serotonergic antidepressant or fluvoxamine- Evidence level B
- 308 ➤ Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- 309 ➤ Reducing the dose of the offending medication - Evidence level C

310 **Anorgasmia –**

- 311 ➤ Switching to agomelatine – Evidence level A
- 312 ➤ Switching to non-serotonergic antidepressant or fluvoxamine- Evidence level B
- 313 ➤ Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- 314 ➤ Reducing the dose of the offending medication - Evidence level C

315 **Erectile dysfunction-**

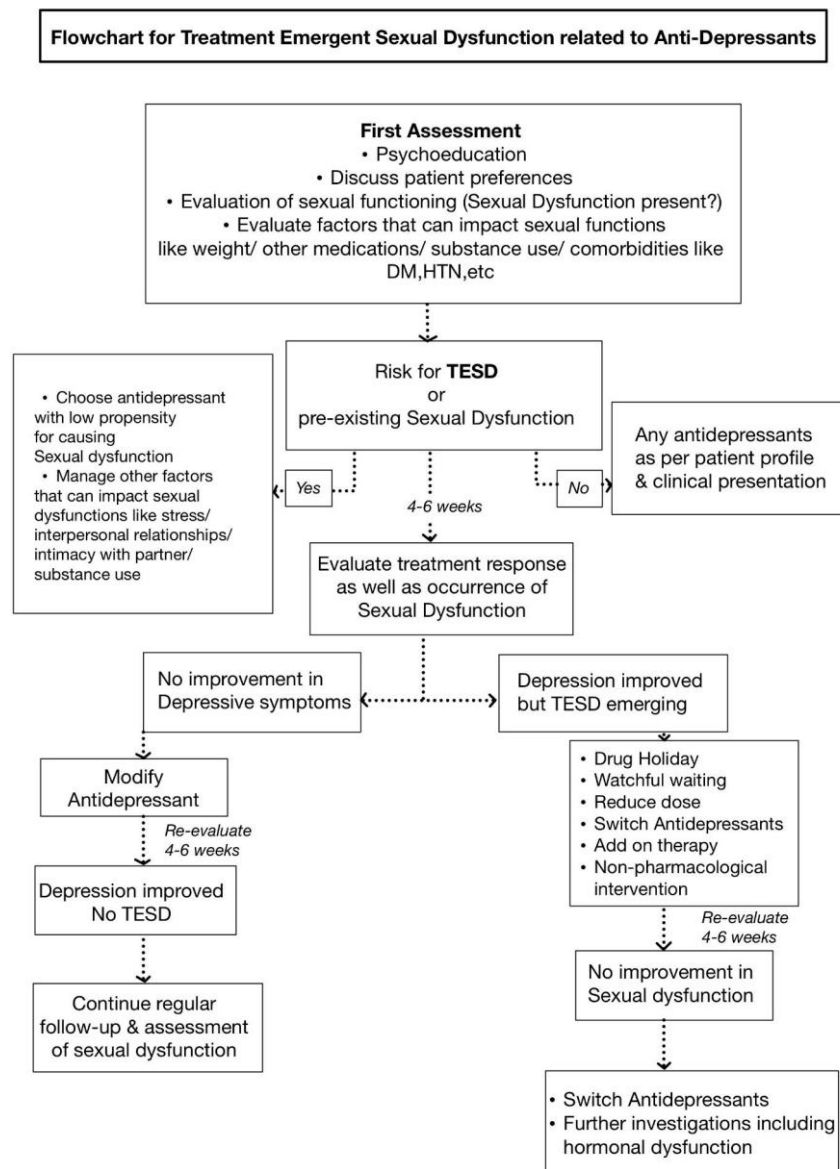
- 316 ➤ Switching to agomelatine – Evidence level A
- 317 ➤ Switching to non-serotonergic antidepressant - Evidence level B
- 318 ➤ Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- 319 ➤ Add PDE5 inhibitors - Evidence level B

320 **Scarce vaginal lubrication-**

- 321 ➤ Switching to agomelatine – Evidence level A
- 322 ➤ Switching to non-serotonergic antidepressant - Evidence level B

- Switching to desvenlafaxine (50 mg/day) or vortioxetine (<15 mg/day)- Evidence level B
- Reducing the dose of the offending medication; vaginal lubricants - Evidence level C

Figure 3: Flowchart for management of TESD related to antidepressants



Box 5

General Principles-

- Comprehensive evaluation to rule out psychiatric or physical comorbidities which may contribute to sexual dysfunction
- To check if the patient is on any other medication or takes any substance which can cause sexual dysfunction.
- If there are symptoms suggestive of hyperprolactinemia, assessment should include measurement of serum prolactin levels.
- Modification of risk factors where feasible (healthy lifestyle, weight management, stress management, treatment of any substance addiction and smoking cessation, physical exercise, relaxation exercises, maintaining good glycemic control in diabetics, treatment of dyslipidemia and hypertension).
- Remaining vigilant about the risk of TESD and ensuring that sexual function is assessed in every follow-up. It is important to remember that patient may not spontaneously complain about sexual dysfunction and it is necessary to ask clear questions.

331 **Pharmacological interventions^[14]**

332 **Waiting for Spontaneous remission of TESD** – If the sexual dysfunction is consequent to the severity
 333 of psychosis, treatment of the disorder can hypothetically improve sexual functioning. Very few studies
 334 have reported spontaneous improvement in antipsychotic related TESD over time and this strategy is
 335 not recommended as sexual dysfunction may persist, leading to treatment non adherence.

336 **Dose reduction^[14]**

337 Reducing the dose of the antipsychotic to the minimum effective dose can be beneficial in improving
 338 SD in some cases. However, the correlation between antipsychotic dosage and sexual dysfunction is
 339 not absolutely certain and there can be a lot of individual variability. Reducing the dosage can
 340 precipitate relapse of illness and this strategy can only be attempted who have been stable for some
 341 time. The treatment regimen should be simplified and other drugs like sedatives and anticholinergics
 342 which can influence sexual functioning should be taken into account when considering TESD. The
 343 treatment plan has to be customized for each patient, taking into account the risk-benefit ratio and
 344 patient and partner preferences.

345 **Switching^[14]**

346 If the patient has severe SD and reducing the dosage is not feasible, one strategy is to switch to an
 347 antipsychotic with less propensity for causing SD.

348 The most robust evidence for switching is for aripiprazole. Multiple studies have demonstrated that
 349 aripiprazole at around dose range of 15 mg/day improves SD (desire, arousal and orgasm) and switch
 350 to aripiprazole from other antipsychotics like risperidone, quetiapine, amisulpride, olanzapine,
 351 clozapine, paliperidone and typical antipsychotics reduces prolactin levels ^[52-55]. Among the newer
 352 drugs, Brexpiprazole, a metabolite of aripiprazole has shown promising results in reducing prolactin
 353 levels in clinical trials, but further research is needed.

354 Olanzapine, which acts by strong 5HT_{2A} antagonism and moderate D₂ and 5HT_{2C} antagonism, causes
 355 hyperprolactinemia at doses above 15 mg/day. At lower doses, it causes less sexual dysfunction
 356 compared to risperidone and haloperidol. ^[56-58]

357 Dopamine agonists can be used to manage the hyperprolactinemia caused by antipsychotics.
358 Cabergoline (0.125-0.250mg/week) ^[59] and bromocriptine (2.5-10mg/day) ^[60] when used prudently has
359 been shown to reverse antipsychotic induced hyperprolactinemia and improve sexual functioning.
360 However, dopaminergic drugs need to be administered with caution as they can exacerbate psychosis.
361 Few small studies have reported benefits after switching to ziprasidone and lurasidone but the quality
362 of evidence is poor.

363 **Adjunctive treatments**

364 When dose reduction or switching is not feasible, one option is to add an adjunctive medication to
365 improve the SD. Multiple randomized studies have shown that adding aripiprazole to the existing
366 antipsychotic can improve SD as well as reduce prolactin level, probably via its partial dopaminergic
367 agonism. It is well tolerated as an add-on drug and the dose can be tailored as per the patient's
368 requirement. ^[53-55]

369 Phosphodiesterase-5 (PDE-5) inhibitors can be used to manage antipsychotic induced erectile
370 dysfunction in males. PDE-5 inhibitors act by enhancing penile vasodilation and targeting the nitric
371 oxide inhibition caused by some antipsychotics. Small randomized control trials have reported good
372 results with sildenafil, tadalafil and vardenafil. ^[61-63]

Box 6

Non-Pharmacological interventions

- Psychoeducation of patient and partner – Patients with psychosis can have widely variable clinical presentation, sexual functioning and treatment response and in each case, the approach has to be customized. In an acutely psychotic patient, stabilization of psychotic may take precedence over assessment of sexual functioning. Once TESD occurs, it may not always be possible to fully restore previous levels of sexual functioning. The treatment approach should try to bring about an acceptable balance between treatment of psychiatric symptoms and sexual functioning, taking into account patient preferences. Psychoeducation about possible adverse sexual side effects of antipsychotics, addressing concerns about reversibility and impact on relationship will be reassuring for the patient and partner.
- Clarify myths/misconceptions about sexuality
- Lifestyle modification, weight management, exercise, focusing on partner intimacy and interpersonal relationships, stress management.
- Specific therapies like dual sex therapy, CBT (to address maladaptive beliefs), mindfulness - based exercises can be used.

373 **Clinical Recommendations** ^[14]

374 Initiate treatment with antipsychotics that have less propensity for causing SD. Aripiprazole, quetiapine,
375 ziprasidone, and olanzapine <15mg/day can be chosen. Avoid risperidone, paliperidone, amisulpride,
376 and typical antipsychotics as first choice if sexual dysfunction is a concern.

378 **If TESD develops, the following are the options** ^[14]

379 A: Recommended (good evidence that the measure is effective, and the benefits far outweigh the
380 harms).

381 B: Recommended (at least moderate evidence that the measure is effective, and the benefits outweigh
382 the harms).

383 C: Neither recommended nor inadvisable (at least moderate evidence that the measure is effective;
384 however, the level of benefit is very similar to the level of harm and a general recommendation cannot
385 be justified)

386 **Low sexual desire-**

387 ➤ Switching to aripiprazole – Evidence level A

- 388 ➤ Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level
- 389 B
- 390 ➤ Adding aripiprazole - Evidence level B
- 391 ➤ Switching to olanzapine <15mg/day - Evidence level B
- 392 ➤ Reducing the dose of the offending medication - Evidence level C

393 **Orgasm retardation –**

- 394 ➤ Switching to aripiprazole – Evidence level A
- 395 ➤ Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level
- 396 B
- 397 ➤ Adding aripiprazole - Evidence level B
- 398 ➤ Switching to olanzapine <15mg/day - Evidence level B
- 399 ➤ Reducing the dose of the offending medication - Evidence level C

400 **Anorgasmia –**

- 401 ➤ Switching to aripiprazole – Evidence level A
- 402 ➤ Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level
- 403 B
- 404 ➤ Adding aripiprazole - Evidence level B
- 405 ➤ Switching to olanzapine <15mg/day - Evidence level B
- 406 ➤ Reducing the dose of the offending medication - Evidence level C

407 **Erectile dysfunction-**

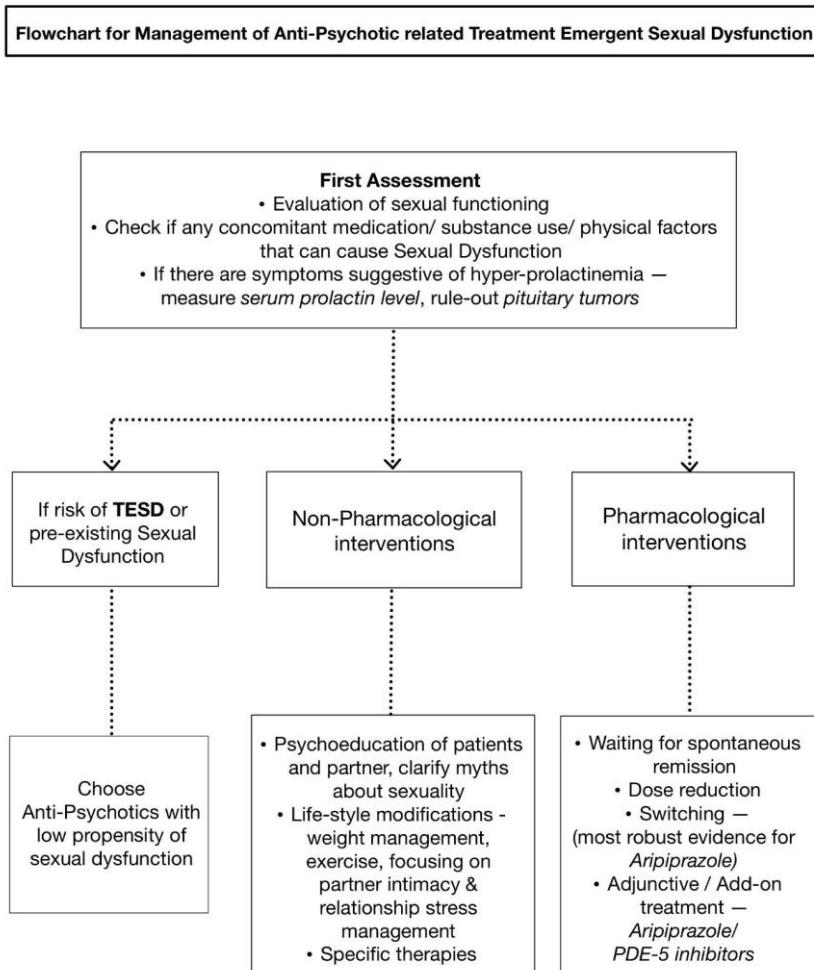
- 408 ➤ Switching to aripiprazole – Evidence level A
- 409 ➤ Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level
- 410 B
- 411 ➤ Adding PDE5 inhibitors - Evidence level B
- 412 ➤ Switching to olanzapine <15mg/day - Evidence level B
- 413 ➤ Reducing the dose of the offending medication - Evidence level C

414 **Scarce vaginal lubrication-**

- 415 ➤ Switching to aripiprazole – Evidence level A
- 416 ➤ Switching to non-hyperprolactinemic Antipsychotics (quetiapine, ziprasidone) - Evidence level
- 417 B
- 418 ➤ Using vaginal lubricants - Evidence level B
- 419 ➤ Switching to olanzapine <15mg/day - Evidence level B
- 420 ➤ Reducing the dose of the offending medication - Evidence level C

421
422

423 **Figure 4: Flowchart for management of TESD related to antipsychotics**



424
425 **Management of TESD related to mood stabilizers**

426 Robust literature on management of TESD associated with mood stabilizers is lacking. Some of the
427 general strategies for management of TESD may be used like switching to drugs with low risk for TESD
428 like lamotrigine, using the minimum effective dose and addition of adjunctive medications. Switching
429 to lamotrigine as well as addition of lamotrigine to carbamazepine or valproate has shown improvement
430 in sexual functioning.^[64,65] Switching to lamotrigine or oxcarbazepine from valproate or carbamazepine
431 has also shown benefit in sexual functioning.^[19] In males on lithium, erectile dysfunction improved on

432 addition of aspirin in a small RCT. ^[66] Literature on the adjunctive use of PDE5 inhibitors in patients
 433 on mood stabilizers is lacking.

434 **Treatment emergent sexual dysfunction associated with non- psychotropic drugs**

435 Treatment emergent sexual dysfunction is a common but underrecognized adverse effect of many non-
 436 psychotropic medications used for the treatment of common medical conditions. In particular, erectile
 437 dysfunction has been reported extensively with many classes of prescription drugs. Recognizing the
 438 risk of drug induced sexual dysfunction and their negative effect on treatment compliance will help the
 439 clinician to tailor the treatment as per the patient's needs and preferences. The table provided below
 440 gives an overview of the various classes of non- psychotropic drugs associated with sexual dysfunction.
 441

Class of drugs	Higher risk	Lower risk/neutral	Comments
Antihypertensives ^[67-70]	- Non- selective beta blockers (Propranolol, Nadolol, Timolol) - Older beta blockers (Metoprolol, Atenolol) - Centrally acting agents (α-Methyldopa, Clonidine, Reserpine) - Thiazide diuretics (especially hydrochlorthiazide)	- Angiotensin Converting Enzyme (ACE) inhibitors (Enalapril, Ramipril, Perindopril) - Angiotensin II receptor blockers (ARBs) (Losartan, Telmisartan, Valsartan) - Calcium channel blockers (Amlodipine, Diltiazem) - Alpha-blockers - Newer beta blockers (Nebivolol)	- ARBs and Nebivolol have the best evidence for preserving/ improving erectile function. - Nebivolol may increase peripheral nitric oxide availability and may improve erectile function. - There is inconclusive evidence regarding negative impact of thiazides in recent literature.
Drugs used for treatment of Congestive Cardiac failure/ ischemic heart disease/arrhythmia ^[67, 71-73]	- Loop diuretics - Thiazide diuretics - Spironolactone - Digoxin - Non- selective and older beta blockers	- ACE inhibitors - ARBs - Nebivolol - Mineralocorticoid receptor antagonist (Eplerenone)	Eplerenone has substantially less endocrine toxicity
Drugs used for the treatment of diabetes mellitus ^[74, 75]	Sulfonyl ureas (Inconclusive evidence)	- Metformin - Dipeptidyl peptidase 4 (DPP-4) inhibitors (Sitagliptin,	- Optimum glycaemic control itself is associated with better sexual function. - GLP-1 agonists and SGLT-2 inhibitors may improve

		Vildagliptin, Linagliptin) • Glucagon like peptide 1 receptor agonists (GLP-1-RA) (Semaglutide, Liraglutide) • Sodium-glucose co-transporter2 inhibitors (SGLT2i) (Dapagliflozin, Empagliflozin, Canagliflozin, Remogliflozin) • Thiazolidinediones	sexual functioning through weight loss and cardiometabolic benefits.
Lipid lowering drugs ^[76-78]		• Statins • Fibrates	• Inconclusive evidence. • Earlier studies suggested that both statins and fibrates can cause ED. • Recent studies indicate improvement of sexual function with statins by improving endothelial nitric oxide synthase activity and increasing nitric oxide bioavailability while subgroup analysis reported increased ED risk with lipophilic statins compared to hydrophilic rosuvastatin.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) ^[72, 79]		• Regular NSAID use especially Aspirin linked to ED	Inconclusive evidence
Gonadotropin-releasing hormone (GnRH) analogues ^[80-82]	GnRH agonists GnRH antagonists		Both GnRH agonists & antagonists reduce levels of luteinizing hormone and follicle-stimulating hormones, which in turn lowers testosterone to castrate levels. Used to reduce gonadotropin levels in central precocious puberty

Contraceptive drugs ^[83, 84]		Hormonal contraceptives linked to low desire and reduced lubrication in few studies	- For low desire switching from hormonal to non-hormonal, from oral to non-oral or from estrogen-containing to no-estrogen-containing forms of contraception. - In case of contraception-related reduced lubrication or Vulvo vaginal atrophy, switch from hormonal to non-hormonal or from oral to non-oral forms of contraception; in addition, a switch to Combined oral contraceptives with higher ethinylestradiol doses may be beneficial
H ₂ Antagonist Antacids ^[85, 86]	Cimetidine	Ranitidine	Cimetidine causes direct androgen receptor blockade, testosterone synthesis inhibition and can cause gynaecomastia
Steroids ^[87-89]	Anabolic androgenic steroids (AAS) Glucocorticoids		AAS suppresses Hypothalamo-pituitary-gonadal axis, causing hypogonadism, reduced libido, erectile dysfunction, gynecomastia, and impaired spermatogenesis Glucocorticoid treatment can reduce sexual desire and cause erectile dysfunction
5 alpha reductase inhibitors ^[90]	Finasteride Dutasteride		Both finasteride and dutasteride can cause impotence, reduced libido, and ejaculation disturbances. Post-finasteride Syndrome (PFS), describes a host of sexual, physical, and neurologic symptoms associated with 5-ARIs that can persist after stopping the drug
Antiretroviral therapy ^[91-94]		Protease inhibitors Dolutegravir (HIV 1 integrase inhibitor)	Mixed evidence Association between ED and protease inhibitors can be caused by induced neuropathy (indinavir), effects on sex hormone metabolism

			(ritonavir) or indirectly due to concomitant medications. Dolutegravir can cause ED and reduced desire in males.
Antifungal agents [95-96]	Azole antifungals		Azole antifungals especially ketoconazole can lead to gynecomastia, decreased libido, oligospermia, azoospermia, impotence
Immunosuppressive drugs ^[97]	Rapamycin inhibitors (Sirolimus Everolimus)		Rapamycin inhibitors (TOR I) reduces testosterone levels and impairs spermatogenesis
Opioid analgesics ^[98]	Oxycodone		Oxycodone is a mu opioid receptor agonist that inhibits ascending pain pathways and can cause ED. Opioids can disrupt the hypothalamic-pituitary gonadal axis by binding to m receptors in the hypothalamus leading to negative feedback, decreased gonadotropins and secondary hypogonadism.

Table 5 Non psychotropic drugs associated with sexual dysfunction

Strategies to manage sexual dysfunction associated with non-psychotropic drugs

- Psychoeducation- Sexual dysfunction can be multifactorial and arise due to the disease process itself or as a consequence of medication. Patients with chronic illnesses may often be unaware that sexual dysfunction has developed as a consequence of their treatment. On the other hand, others may blame their drugs for sexual problems which have occurred due to psychosocial factors. In each case, the sexual functioning of the patient has to be considered when planning the treatment.
- Switching to an alternative drug with less potential for causing sexual dysfunction
- In men, phosphodiesterase type 5 inhibitor in anticipation of intercourse (contraindicated if the patient is on nitrates).

Comparison of various phosphodiesterase 5 inhibitors for erectile dysfunction^[99]

Drug name	Sildenafil	Tadalafil	Vardenafil	Avanafil
Timing of dose	60 minutes prior	At least 30 minutes prior	25-60 minutes prior	15-30 minutes prior

Max plasma concentration	30-120 minutes Median 60 minutes	30-360 minutes Median 120 minutes	30-120 minutes Median 60 minutes	30-120 minutes Median 30-45 minutes
Half life	3-5 hours	17.5 hours (healthy men) 21.6 hours (elderly men)	4-5 hours	3-5 hours
Daily dosing	No	Yes	No	No
Available doses in mg	25, 50, 100	2.5, 5, 10, 20	2.5, 5, 10, 20	50, 100, 200
Recommended starting doses in mg/day	50	10	10	100
Maximum dose in mg/day	100	20	20	200
Affected by fatty meal	Yes	No	Yes	Yes
Side effects	Rhinitis, dyspepsia, headache, flushing, vision changes	Headache, dyspepsia, back pain, myalgia, nasal congestion, flushing, and pain in limb	Headache, flushing, rhinitis, dyspepsia	Headache, flushing, nasopharyngitis, nasal congestion
Contraindications	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet	Concomitant use of any form of organic nitrate Hypersensitivity to any component of the tablet

Conclusion

Treatment emergent sexual dysfunction is a clinically relevant and often unrecognized adverse effect of psychotropic as well as non-psychotropic medications. It can have a significant negative impact on quality of life, interpersonal relationships, self-esteem, and most alarmingly, treatment adherence. Patients are often reluctant to disclose sexual problems spontaneously. Clinicians need to be cognizant of these concerns and evaluate sexual functioning with sensitivity by using validated tools. Sexual functioning assessment should be part of the routine clinical evaluation throughout the course of the treatment. Assessment where TESD is suspected should be comprehensive and take into account the baseline sexual functioning, physical examination, temporal relationship with the offending drug, dose and duration of exposure, concomitant medications, substance use, medical comorbidities and relationship or psychosocial factors. Management should follow a patient-centered, risk-benefit approach, taking into account the patient/partner preferences. If possible, selection of agents with a lower propensity for sexual adverse effects should be considered in patients for whom sexual functioning is an important treatment priority. Once dysfunction develops, management may include

470 modification of contributing factors, dose optimization, switching to an alternative medication with a
471 more favourable sexual adverse-effect profile, or addition of an appropriate symptomatic treatment.
472 Such decisions should take into account the severity and persistence of sexual dysfunction, the response
473 to the primary treatment, relapse risk, comorbidities, drug interactions and patient preferences. Non
474 pharmacological interventions like psychoeducation, modification of risk factors where possible and
475 specific psychotherapies if indicated are important. To reiterate, sexual side effects should be taken into
476 account when considering the pros and cons of different treatment modalities. Enquiring proactively,
477 assessing systematically, identifying reversible contributors, discussing options openly with the patient,
478 and individualizing treatment according to the balance between psychiatric/medical benefit and sexual
479 adverse effects remains integral to good clinical practice.

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