Sexual Dysfunction with Antidepressants: A Clinical Review

Shorouq Motwani1, Anita Hukumchand2, Sagar Karia3, Sushma Sonavane4, Avinash Desouza5

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ABSTRACT

Sexual dysfunction is an important unwanted phenomenon of psychotropic medications. This is often underreported and not given due importance, which can often lead to impaired quality of life and less-than-optimal medication compliance. All types of psychotropic medications are linked to sexual side effects. As the underlying mental disorder improves, some of the sexual issues abate, but treatment-related sexual adverse effects may persist over time and are unfortunately underrecognized by clinicians and scarcely investigated in clinical trials. When it comes to sexual dysfunction due to psychiatric disorders, there are two important things to understand. First, any mental illness can cause sexual dysfunction, and second, severer the underlying psychiatric disorder, severer is the sexual dysfunction (in both frequency and severity). Even though patients may be suffering from mental illnesses of variable severity, it is important for them to have a normal and enjoyable sex life. The reported incidence of sexual dysfunction found with antidepressant medication varies considerably between different studies, making it difficult to estimate the exact incidence or prevalence. The sexual problems encompass a range of sexual disorders and include decreased sexual desire, decreased sexual excitement, diminished or delayed orgasm, and erection or delayed ejaculation problems. Patients with sexual disorders usually also have anxiety disorder and vice versa; also, women with sexual dysfunction are more prone to anxiety and depression compared with others. This happens because sex steroids and the various neurotransmitters modulate both sexual function and mood. The mechanism by which psychotropic medications affect the sexual cycle is through the interaction between medications and the various above-mentioned neurotransmitters. Physicians should monitor their patients for antidepressant-induced sexual adverse effects, as these may affect compliance with therapy and the ultimate treatment success. Sexual function should be actively assessed at regular intervals. Management of antidepressant-induced sexual dysfunction requires an individualized approach.

Keywords: Antidepressants, Erectile dysfunction, Libido, Psychotropics, Sexual dysfunction.

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INTRODUCTION

Psychiatric disorders as a term encompass a multitude of disorders, which can range from neurodevelopmental disorders to substance-related and addictive disorders. Along with the typical features associated with these disorders, often an overlap between different disorders is observed. The most commonly encountered overlap is seen with depressive disorders.1 When we speak of major depressive disorder or dysthymia, the following symptomatology is most often presented:2

- Pervasive sadness of mood
- Easy irritability
- Decreased or increased sleep
- Decreased on increased appetite
- Anhedonia/lack of motivation to do previously pleasurable activities
- Passive death wishes
- Suicidal ideations and/or attempts.

In such cases, it is imperative to evaluate every case on an individual basis and form a management plan to treat not only the presenting illness but also the associated depressive symptoms. When deciding to treat any illness, if the depressive symptoms predominate, a shift in diagnosis is made, and depression becomes our primary target illness.1 When evaluating a patient and formalizing a treatment plan, it is important to keep in mind the mechanism of action of the bouquet of antidepressants. There are 11 general domains where psychotropics generally act: acetylcholine, dopamine, GABA, glutamate, histamine, ion channel, lithium mimetic, melatonin, norepinephrine, opioid, and serotonin, and the mode of action of these medications can also vary. This includes action as a receptor agonist, receptor partial agonist, receptor antagonist, reuptake inhibitor, reuptake inhibitor and releaser, reuptake inhibitor and receptor antagonist, an enzyme inhibitor, ion-channel blocker, positive allosteric modulator (PAM), or enzyme modulator.6

Neurobiological Mechanisms of Sexual Dysfunction with Antidepressants

Keeping antidepressant agents in focus, there is evidence to show that they are probable to cause sexual side effects through their mechanism of action.5 In such scenarios also, there are certain excitatory and inhibitory factors that play a role in the mechanism of action of psychotropics in general. The excitatory factors include dopamine, melancortins, noradrenaline, testosterone, estrogen, and oxytocin, while the inhibitory factors include serotonin, prolactin, and opioids.6

1-5Department of Psychiatry, Lokmanya Tilak Municipal Medical College, Mumbai, Maharashtra, India

Corresponding Author: Sagar Karia, Department of Psychiatry, Lokmanya Tilak Municipal Medical College and Hospital, Mumbai, Maharashtra, India, Phone: +91 9594530457, India, e-mail: kariabhai117@gmail.com

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When we discuss the sexual cycle and the role of antidepressants in altering it, it becomes useful to first understand the physiology of the sexual cycle and the neurotransmitters affecting it. Among the neurotransmitters concerned with psychiatry, the following have a role to play in the sexual response cycle as well. In chronological order, desire is promoted by dopamine, norepinephrine (NE), and estrogen, while it is inhibited by serotonin and prolactin. When it comes to arousal, nitric oxide, dopamine, NE, estrogen and testosterone, oxytocin, acetylcholine, and melanocortin enhance it, while serotonin brings down the arousal. In the stage of orgasm, dopamine and nitric oxide help in enhancing the orgasm while serotonin dampens it. When D1 and D5 receptors are stimulated, they help in facilitating sexual arousal in the form of erection in males and receptivity in females. On stimulation of D2 receptors, orgasm comes to fruition, while serotonin reduces sexual activity by blocking dopamine.7

The mechanism by which psychotropic medications affect the sexual cycle is through the interaction between medications and the various above-mentioned neurotransmitters. Sexual dysfunction occurs with the use of antidepressants because of increases and decreases in the levels of various neurotransmitters caused by these drugs. The main mechanism of action of most antidepressants is through modulation of the levels of neurotransmitters and their receptors in the synapses of the central nervous system.8

Prolactin is a hormone released by the anterior pituitary gland that is responsible for milk production during lactation. However, prolactin also suppresses ovulation and sexual desire and function.9 Antipsychotics cause blockade of dopamine receptors (their mechanism of action), and hence there is an increase in prolactin levels which causes sexual dysfunction.10 Also, one must remember that these medications interact with muscarinic and histaminergic neurotransmitters and receptors too. Delayed ejaculation/orgasm is caused by the use of selective serotonin reuptake inhibitors (SSRIs) – this is due to the increase in serotonin levels produced by these drugs, which interfere with the pathways of ejaculation and erection.8 Tricyclic antidepressants interfere with serotonin, dopamine, noradrenaline, acetylcholine, and other neurotransmitters, all of which contribute to sexual dysfunction.11 Selective serotonin reuptake inhibitors can reduce the function of the hypothalamic–pituitary–testis axis and lower levels of LH, FSH, and testosterone, which leads to impaired sexual function.3

The Sexual Cycle and Sexual Dysfunction

The sexual cycle from desire leading up to orgasm is complex and must be reviewed for a better understanding of how drugs can wreak havoc with this system. Hormones causing increased sexual desire are noradrenaline, dopamine, and estrogen. Those decreasing sexual desire are prolactin and serotonin. The principal chemicals causing arousal are nitric oxide, dopamine, NE, estrogen and testosterone, oxytocin, acetylcholine, and melanocortin. Serotonin causes decreased arousal.12 Orgasm is facilitated by NE, dopamine, and nitric oxide, whereas it is inhibited by serotonin. Different dopamine receptors also play different roles during the sexual cycle. D1 and D5 receptors are responsible for sexual arousal, which facilitates erection and receptivity in females. High activity of dopamine at D2 receptors leads to orgasm.12

Psychiatric diseases and sexual disorders are usually associated with each other. Patients with sexual disorders usually also have an anxiety disorder and vice versa. This happens because sex steroids and the various neurotransmitters modulate both sexual function and mood.13

Sexual Dysfunction and Psychiatric Disorders

When it comes to sexual dysfunction due to psychiatric disorders, there are two important things to understand. First, any mental illness can cause sexual dysfunction, and second, severer the underlying psychiatric disorder, severer is the sexual dysfunction (in both frequency and severity).14 Even though patients may be suffering from mental illnesses of variable severity, it is important for them to have a normal and enjoyable sex life.

Patients may also have other causes for their sexual dysfunction. Neurological diseases like amyotrophic lateral sclerosis, spinal cord injury, and multiple sclerosis should never be ignored, nor should endocrine diseases like diabetes mellitus, hypothyroidism, and adrenal insufficiency.15 Local genitourinary causes should not be missed since they are treatable.

Patients may also be having psychological issues like performance anxiety and dislike for the partner. There may also be issues of improper education about sex and unrealistic expectations.16 It is invaluable to ask about the concurrent use of other nonpsychotropic drugs, like antihypertensives that can cause similar symptoms. Never forget to rule out whether drugs of abuse like cocaine, LSD, marijuana, and others are playing a role.17 It is vital to determine if the symptoms started after a diagnosis of a medical disorder, the addition of a new medicine, a new or traumatic life event, or a change in the life schedule. Among antidepressants, higher risks of sexual dysfunction are seen with SSRIs, SNRIs, TCAs, and MAO inhibitors, with lesser risks with atypical drugs like bupropion, mirtazapine, and agomelatine.5 First-generation antipsychotics are associated with more sexual dysfunction than second-generation and newer drugs. Among second-generation drugs, risperidone, paliperidone, amisulpride, and clozapine are designated high risks, while olanzapine, quetiapine, ziprasidone, and aripiprazole are considered low risk.18 The various side effects seen with these drugs are decreased desire, apathy toward sex, decreased lubrication, genital anesthesia, and anorgasmia. Men may suffer from erectile dysfunction, premature ejaculation, decreased penis size, delayed ejaculation, testicular atrophy, and pain and priapism. Females often report decreased vaginal lubrication, pain during coitus, nipple insensitivity, and irregular menstrual cycles.4

Sexual Dysfunction and Psychotropics

It is important to understand that sexual dysfunction is an important side effect of psychotropic medications. This is often underreported and not given due importance, which can often lead to impaired quality of life and poor medication compliance. All types of psychotropic medications are linked to sexual side effects. As the underlying mental disorder improves, some of the sexual issues abate, but clinicians underrecognize treatment-related sexual adverse effects, and thereby these are scarcely investigated.19

Why Sexual Issues are Underestimated and Ignored in Patients with Psychiatric Disorders?20

- Patients do not have faith in their treating physicians
- They feel ashamed to communicate about sexual issues
- Cultural and language barriers
- Patients not having received sex education and lack of knowledge about sex and its associated problems
- Healthcare providers do not routinely ask about sexual problems
- Lack of time for treating doctors
- Lack of expertise in sexual dysfunction among psychiatrists
- Stigma and taboo associated with the topic
Approach a Patient with Sexual Dysfunction (SD)
One must take a thorough sexual history at the first encounter to know the baseline level of sexual function. Sexual function before the mental illness might need changes in the treatment plan. Sexual dysfunction can result from mental illness, or its psychiatric treatment or SD can also cause mental illness. One must quantify the level of sexual dysfunction at three distinct time periods—before, during, and after treatment. The use of questionnaires that are validated should be encouraged throughout the course of treatment to keep track of worsening or improving sexual function.  

One’s plan of action should depend on the severity of the sexual dysfunction and how much it affects the patient’s quality of life. Many patients have mild-to-no sexual problems with these medicines, while others are not concerned about it. It is useful to directly ask if these sexual side effects have ever caused them to stop their medications. One must also keep a track of sexual side effects after treatment has been stopped since they can be due to other causes that can be treated.  

Managing Sexual Side Effects
The management of sexual side effects due to antidepressants should be individualized and patient-centered. The focus should be on reducing the sexual symptoms and causing maximum benefit to the patient. One approach is to observe and do nothing. Side effects of some medications like SSRIs wane over time and the sexual side effects disappear. Hence the patients will continue to get the benefit of the drug but will not experience any of the side effects. There are studies which show that sexual dysfunction abates in 80% of patients within 6 months. Another strategy that is commonly used is to reduce the medicines. One must reduce the dose to the minimum needed for the desired effect. If the medicine is not absolutely needed, stop the medicine. Reducing the dose, however, can cause relapse of the underlying mental illness and worsen the condition, including sexual symptoms. The patient must be thoroughly educated about this possibility. The clinician should keep close follow-up of the patient and monitor for worsening of the disease status.  

One must also consider the use of drug holidays. There is proof that drug holidays can reduce the side effects from drugs. However, it can lead to withdrawal and worsening of symptoms as well as reduced compliance from the patient’s side. Hence, drug holidays are usually not recommended.  

Switching to a different medication that has a different side-effect profile can also be useful. If SSRIs are causing sexual dysfunction, it makes sense to change to a non-SSRI antidepressant so that the antidepressant effect is maintained, but sexual side effects disappear. There are multiple reports of improvement in sexual function after changing from SSRIs to bupropion. However, we must be cautious because these other medications may have their own unique side effects that can cause even more discomfort to the patient.  

Augmentation Strategies
Augmentation strategies refer to the addition of another medicine to reduce the SD caused by antidepressants. There is good evidence to support the use of bupropion, tamsulosin, phosphodiesterase-5 inhibitors (e.g., sildenafil), testosterone, and 5-HT2 antagonists (e.g., mirtazapine) to treat sexual dysfunction. The advantage of this method is that we will not have to stop the SSRI or antidepressant. There are other nonpharmacological methods that are of proven benefit. Cognitive behavior therapy (CBT), sex therapy, couples’ counseling, acupuncture, meditation, and yoga all provide relaxation and improve sexual function. Other strategies like the use of vibrators and scheduled sexual activity (i.e., in the morning before the daily SSRI dose) can also help the patients.  

When it comes to SD and depression in particular, there are certain points that are worth mentioning. The prevalence of SD in patients of depression is roughly 70–80%. The worse the depression and the longer its duration, the worse the sexual dysfunction. Thus, they have a directly proportional relationship. Depressed patients should be screened for sexual dysfunction, and patients with SD should be screened for depression. Depressed patients have issues concerning mood, energy, interest, capacity for pleasure, self-confidence, and self-esteem. This leads to issues causing decreased sexual desire and interest, decreased and difficult arousal, and inability to maintain erections and reach orgasm, along with decreased vaginal lubrication and painful coitus. Many patients with depression also have anxiety disorder and symptoms of anxiety, which itself is associated with sexual difficulties. Depressed patients also have obsessive and compulsive traits and behaviors. These further reduce sexual pleasure and sexual satisfaction. We understand that antidepressants reduce many aspects of sexual function, but many times it is not appreciated that depression itself can be the root cause of the symptoms. Moreover, comorbid medical and psychiatric disorders are also not considered many times.  

There is a rising trend in the use of antidepressants in children and adolescents. It interferes with sexual and romantic relationships and affects their quality of life, apart from also causing problems with sexual function and relationships later in life. There is also an entity called post-SSRI sexual dysfunction (PSSD), in which patients continue to have side effects from antidepressants after discontinuing them. Paroxetine has the highest side effects followed by fluvoxamine, sertraline, and fluoxetine. Mechanism of action of antidepressants causing sexual dysfunction: ADs that stimulate postsynaptic receptor SHT2A cause a reduction in dopamine in the mesolimbic pleasure centers causing decreased desire. It also increases prolactin causing decreased desire and arousal. These drugs also inhibit the action of nitric oxide (NO), which causes problems in arousal, causing genital anesthesia, inhibiting medullary reflex and the orgasm. Drugs with anticholinergic effects like TCAs inhibit parasympathetic excitement. They also have antagonism at alpha-1 adrenergic receptors causing inhibition of ejaculation. Some drugs also have antihistaminic effects, which cause drowsiness, so this ultimately undermines desire and arousal. The antidepressants that cause less sexual dysfunction are—bupropion, agomelatine, vortioxetine, and vilazodone – they have some effect of dopamine stimulation. Mirtazapine and nefazodone cause antagonism at the postsynaptic receptor SHT2A. Moclobemide causes less sexual dysfunction because it also leads to an increase in the levels of dopamine and noradrenaline, which somewhat offset the increase in serotonin. Reboxetine has noradrenergic effects, so it causes less SD. Tianeptine stimulates dopamine release and does not have any stimulatory effects on the serotonin receptor.  

It has been observed that there is less sexual dysfunction associated with the use of agomelatine, aminetine, bupropion, moclobemide, mirtazapine, or nefazodone. Bupropion is associated with a significantly lower rate of treatment-emergent sexual dysfunction than the SSRIs and SNRIs – escitalopram,
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Fluoxetine, paroxetine, sertraline, and venlafaxine. It is also true that mirtazapine has much less sexual side effects than the other antidepressants. New multimodal drugs work by multiple mechanisms of action. One among them is vilazodone. Vilazodone appears to have a low incidence of spontaneously adverse effects on sexual function. One study evaluated reasons for missed dosages of antidepressants. They found that decreased libido and sexual dysfunction were consistently among the top five reasons for noncompliance.5

**Treatment for Sexual Dysfunction by Antidepressants**

**Premature Ejaculation**

Behavioral therapy is and should be the primary therapy for premature ejaculation in most patients. In terms of medications, tricyclic antidepressants such as clomipramine or SSRIs are helpful in persistent problems. The short-acting SSRI dapoxetine is effective in treating premature ejaculation, with either daily dosing or “on-demand” dosage. It is usually combined with tadafalif and can be given at an on-demand dosage. Dapoxetine has similar efficacy to paroxetine, though it may be less well-tolerated.27

**Erectile Dysfunction**

Trazodone, known to be a partial agonist at 5-HT1A receptors and antagonist at 5-HT2A and alpha-1 adrenergic receptors, is useful in reducing “psychogenic” erectile dysfunction when prescribed at a higher daily dosage (150–200 mg).28

Though patients experiencing “treatment-emergent” sexual side effects are quite common, but an antidepressant reduces depressive symptoms which improves sexual desire and satisfaction. Thus, patients who respond to antidepressant treatment also show improvement in sexual function.

**Management of Sexual Side Effects Caused by Antidepressants**

- An antidepressant known to cause less sexual side effects would be an ideal choice in a patient who already reports sexual dysfunction due to depression.

- Most sexual side effects caused by antidepressants are dose-related, hence patients usually report relief in side effects once the dose of antidepressants is brought down.29

- While remaining cautious about a relapse in symptoms or a discontinuation syndrome, a well-designed drug holiday, that is, regular brief interruptions in treatment can be attempted.

- A switch from an agent causing significant sexual side effects to an agent less probable to cause sexual side effects can be tried again with caution to avoid a relapse in depressive symptoms or discontinuation syndrome from the first agent. Sexual side effects seem to be less common with norepinephrine and dopamine reuptake inhibitors (NRIs) or norepinephrine reuptake inhibitors (NRIs). Other therapeutic treatments that do not lead to antidepressant-induced sexual dysfunction include buspirone, trazodone, and nefazodone. Trazodone and nefazodone: these are serotonin antagonists and reuptake inhibitors (SARI). Their antagonism of the SHT2A receptor is thought to result in less interference with sexual pleasure.24

Antidepressants with the lowest rate of sexual side effects include bupropion, mirtazapine, vilazodone, and vortioxetine.8

- **Adjunct medications:** Phosphodiesterase-5 inhibitors such as sildenafil and tadafalif, testosterone gel, bupropion, methylphenidate, and olanzapine are some agents that can help in curbing the sexual side effects. Aripiprazole is known to improve sexual interest and satisfaction in depressed women, and this is independent of its antidepressant effects.30

  - **Naturapathic remedies:** Gingko biloba, Yohimbe, Saffron, Maca root, and Rosa Damascena oil along with acupuncture have some case reports showing a benefit with reducing sexual dysfunction.31

  - **Lifestyle modifications:** Exercise prior to sexual activity improves sexual desire and global sexual functioning in depressed women taking antidepressants, timing sexual activity in accordance with medication intake and psychotherapy, or couples counseling or some sort of sexual stimulation such as visual or vibratory stimuli that can facilitate sexual activity in a patient on antidepressants with sexual side effects.32

- **Attenuating agents:** Drugs like cyproheptadine which are anti-histamine and anti-serotonin (5HT2 inhibition), help in attenuating antidepressant-caused sexual dysfunction. Use of cyproheptadine 1–2 hours before intercourse (4–16 mg) regularly or on-demand was found to improve sexual function, particularly improvement was noted in libido and orgasm, thus making it helpful in primary anorgasmia by decreasing ejaculation latency, thus improving delayed ejaculation. It is effective both when taken before sex or on a regular basis.33

- **Gender-specific antidote agents:** Placebo-controlled trials suggest that buspirone, bupropion, and sildenafil are adjunctive/augmenting agents that can be used in women. Estrogen and testosterone hormones also play a role in women. Bupropion, sildenafil, and hormone testosterone also play a role as adjunctive/augmenting agents in antidepressant-induced sexual dysfunction in men. Certain potential adjunctive/augmenting agents that could be used for both genders include yohimbine, amantadine, psychostimulant agents, cyproheptadine, pramipexole, and ropinrole.34

**Conclusion**

Sexual dysfunction is a common adverse effect of antidepressant treatment, which physicians should monitor as it may affect compliance with therapy and ultimate treatment success. Also, monitoring these side effects will enable physicians to treat them at the earliest. Sexual function should be actively assessed at baseline, at regular intervals during treatment with an antidepressant, and after treatment cessation. Management of antidepressant-induced sexual dysfunction requires an individualized approach.

**References**


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