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How do SSRIs cause sexual dysfunction?

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Understanding key mechanisms can help improve patient adherence, prognosis

Although selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed[1] and are better tolerated than older antidepressants, side effects such as sexual dysfunction limit patient acceptance of these medications. DSM-IV-TR categorizes medication-induced sexual dysfunction as a type of substance-induced sexual dysfunction.[2] These dysfunctions are characterized by impairment of various sexual response phases (***Table 1***).[2,3]

Estimating the true incidence and prevalence of SSRI-related sexual dysfunction can be difficult. Zimmerman et al[4] compared psychiatrists' clinical assessments of depressed patients receiving ongoing treatment with results of a standardized side effects questionnaire and found that even though psychiatrists regularly inquired about sexual side effects, on the questionnaire patients reported higher rates of almost all sexual dysfunctions. The incidence of SSRI-induced sexual dysfunction also can be difficult to ascertain because some sexual dysfunctions frequently accompany a primary psychiatric disorder[5] or physical illness. Balon[6] suggested that the incidence of SSRI-associated sexual dysfunction is 30% to 50%, although others have reported higher incidences.

Few quality studies have focused on identifying the exact nature and causes of SSRI treatment-emergent sexual dysfunction. This article describes mechanisms that may be fundamental to SSRI-associated sexual dysfunction.

Not just serotonin

Although SSRIs are relatively selective for the serotonergic system, they affect other neurotransmitter systems

Table 1

Sexual dysfunction and the sexual response cycle

Phase	Description	Dysfunction/disorder
Desire	Characterized by sexual fantasies and the desire to have sex	Hypoactive sexual desire disorder
		Sexual aversion disorder
		Hypoactive sexual desire disorder due to a general medical condition
		Substance-induced sexual dysfunction with impaired desire
Excitement	Subjective sense of sexual pleasure and accompanying physiologic changes	Female sexual arousal disorder
		Erectile disorder
		Erectile disorder due to a general medical condition
		Dyspareunia due to a general medical condition
		Substance-induced sexual dysfunction with impaired arousal
Orgasm	Peaking of sexual pleasure with release of sexual tension	Female orgasmic disorder
		Male orgasmic disorder
		Premature ejaculation
		Other sexual dysfunction due to a general medical condition
		Substance-induced sexual dysfunction with impaired orgasm
Resolution	A sense of general relaxation, well-being, and muscle relaxation	Postcoital dysphoria
		Postcoital headache

Source: References 2,3

as well (***Table 2, page 32***).[7] For example, at high dosages paroxetine is believed to block norepinephrine reuptake, and it has a clinically significant anticholinergic effect. Also, sertraline is a potent reuptake inhibitor of dopamine.[8] Therefore, our discussion will include these neurotransmitters.

In their dual control model of male sexual response, Bancroft et al[9] discuss the interplay between excitatory and inhibitory mechanisms at the central and peripheral levels. For example, they describe the role of norepinephrine mediation in the central arousal system via the disinhibition of dopaminergic and a possible testosterone mechanism. They also point to possible inhibition of central sexual arousal by neuropeptidergic and serotonergic mechanisms.

Evidence linking serotonin to sexual dysfunction is inconclusive because there are no exclusively serotonergic agents. Drugs frequently used to test these hypotheses often affect other neurotransmitters, which means conclusions are not specific to serotonin. Animal studies of the impact of serotonin agonist and antagonist agents on mounting and ejaculation have reported inconsistent results.[10] Differential roles of 5-HT1 and 5-HT2 receptor activation on sexual behavior may explain some of these inconsistencies.[8] However, 1 study found that antiserotonergic pharmacologic agents enhance sexual excitation in laboratory animals,[11] and a separate study showed that severing serotonergic axons in the medial forebrain bundle in male rats facilitated ejaculation.[12]

Monteiro et al[13] found a high incidence of anorgasmia in previously orgasmic patients after they received clomipramine, which may be partially attributed to the drug's serotonergic action. This prompted researchers to hypothesize that central serotonergic tone inhibits sexual behavior. However, based on current evidence, it would be best to consider serotonin as having a modulating effect[10]—as opposed to a complete inhibitory effect—on human sexual behavior.

Regarding the parasympathetic system,

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Although SSRIs are relatively selective for serotonin, they also affect other neurotransmitter systems

SSRIs and sexual dysfunction

Clinical Point

SSRIs may reduce levels of nitric oxide, which is necessary for mediating penile vasculature changes needed for erection

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Table 2

Neurotransmitters affected by SSRIs

SSRI	Neurotransmitters
Citalopram	5-HT
Escitalopram	5-HT
Fluoxetine	5-HT, NE, DA
Fluvoxamine	5-HT
Paroxetine	5-HT, NE, Ach
Sertraline	5-HT, NE, DA

5-HT: serotonin; Ach: acetylcholine; DA: dopamine; NE: norepinephrine; SSRIs: selective serotonin reuptake inhibitors

Source: Reference 7

it was long believed that cholinergic innervations mediate penile erection. However, a more plausible hypothesis may be that parasympathetic cholinergic transmission at best has a modulating effect when other neurotransmitters—primarily the adrenergic system—are affected by concomitant pharmacologic interventions. Segraves[10] proposed that cholinergic potentiating of adrenergic activity may be primarily responsible for bethanechol-induced reversal of SSRI-induced sexual dysfunction.

The adrenergic system is believed to play a role in penile erection and ejaculation.[10] Adrenergic fibers innervate the vas deferens, seminal vesicles, trigone of the urinary bladder, and proximal urethra.[14] Penile contractile and erectile tissue is richly innervated by the adrenergic nerve fibers.[10] Ejaculation is mediated by α1-adrenergic receptors.[10]

The role of nitric oxide synthase

The advent of sildenafil underscored the importance of nitric oxide-mediated relaxation pathways in treating erectile dysfunction. Nitric oxide plays an important role in mediating the penile vasculature changes essential for erection and also is hypothesized to promote penile smooth muscle relaxation via cyclic guanosine monophosphate, thereby contributing to physiologic erection.[15] Paroxetine is known to inhibit nitric oxide synthase, which reduces nitric oxide levels. The exact mechanism of this interaction remains unclear; however, it is hypothesized that 3 nitric oxide synthase isoenzymes are structurally similar to cytochrome P450 (CYP450). Paroxetine is a strong CYP2D6 inhibitor, which contributes to low nitric oxide levels in patients taking the drug.[16]

SSRIs and sexual response

Because decreased libido is part of depressive psychopathology,[5] it is difficult to attribute loss of sexual desire directly to SSRIs. Nonetheless, SSRIs are associated with a risk of clinically significant loss of sexual desire that may resemble moderate to severe hypoactive sexual desire disorder.[17] Reduced mesolimbic dopaminergic activity as a result of inhibitory serotonergic midbrain raphe nuclei projections is 1 possible cause.[18] This hypothesis has lead investigators to examine drug targets in the CNS for hypoactive sexual desire disorder that would inhibit serotonergic tone and lead to brain dopaminergic system stimulation.

Another putative hypothesis for SSRI-induced loss of sexual desire is the role of 5-HT1A receptor-mediated norepinephrine neurotransmission. Because the sympathetic nervous system is believed to be involved in genital arousal in women, a small study analyzed the effect of sympathetic activation on SSRI-induced sexual dysfunction.[19] Women who received paroxetine and sertraline—both are highly selective for 5-HT1A—showed improvement in sexual arousal and orgasm after taking ephedrine before sexual activity.[19] Women who took fluoxetine, which is less selective for 5-HT1A, show no change or decreased sexual function.

SSRIs are associated with reduced nocturnal penile erections and severe erectile dysfunction, but the relationship is not robust.[17] SSRI-induced suppression of rapid eye movement sleep[20] may partially explain reduced nocturnal and early morning erections. Supraspinal areas and preganglionic sacral neurons involved in sexual excitement also are reported to have substantial serotonergic activity, which suggests that serotonin has a direct role in erectile dysfunction at a comparative peripheral level.[21] However, a recent study[17] found no difference in flaccid and peak systolic velocity when comparing patients taking SSRIs with those who do not. This indicates that SSRIs'

affect on spontaneous and sexually aroused erections may be mediated at both central and peripheral levels.

Delayed ejaculation frequently is associated with SSRIs[17] and usually is not caused by depressive psychopathology.[22] Animal studies show that increased serotonergic tone predicts ejaculatory latency by acting as an inhibitor at the hypothalamus level.[23] In contrast, noradrenergic tone enhances ejaculation.[24] Antidepressants that increase noradrenaline levels and serotonin levels—such as serotonin-norepinephrine reuptake inhibitors—induce milder ejaculatory delay.[17]

A recent study[17] found impaired climax and reduced libido in partners of patients using SSRIs. Patients receiving SSRIs report less frequent sexual intercourse and heightened guilt associated with masturbation, and SSRIs are associated with psychosocial factors such as higher stress at work and increased risk of conflicts with partners and other family members.[17] In addition to biologic mechanisms, these psychosocial and intra-couple factors might contribute to SSRI-associated sexual dysfunction. However, because the temporal association between SSRI use and psychosocial dysfunction is ambiguous, this hypothesis should be interpreted with caution.

SSRIs have been associated with lower serum levels of luteinizing hormone, follicle-stimulating hormone, and testosterone.[25] However, these findings need to be replicated before drawing firm conclusions on intermediary role of hormones in SSRI-emergent sexual dysfunction.

Be aware that other medications may contribute to sexual dysfunction experienced by a patient receiving an SSRI (***Table 3***).[26]

SSRIs for premature ejaculation?

Because SSRIs can cause delayed ejaculation, they have been used off-label to treat premature ejaculation.[27] For this purpose, paroxetine and sertraline have been prescribed with daily or on-demand dosing before sexual intercourse[28] and daily fluoxetine has been used.[29] However, none of these SSRIs is FDA-approved for treating premature ejaculation, daily dosing of SSRIs exposes patients to undesirable side effects, and inconsistent use of paroxetine can lead to discontinuation syndrome.

These concerns have lead researchers to seek an SSRI that could be used on as-needed basis and would not cause some of the deleterious side effects associated with current SSRIs. The short-acting SSRI dapoxetine is in FDA review for treating premature ejaculation; the drug is approved for this use in several countries outside the United States.[30]

Table 3

Other than SSRIs, which medications can cause sexual dysfunction?

Psychotropics
Amphetamines
Anticonvulsants
Antidepressants • serotonin-norepinephrine reuptake inhibitors • tricyclic antidepressants • monoamine oxidase inhibitors
Antipsychotics
Benzodiazepines
Nonpsychotropics
Antihypertensives • alpha blockers • beta blockers • diuretics
Digoxin
Histamine blockers
Lipid-lowering agents
Narcotics
Oral contraceptives

SSRIs: selective serotonin reuptake inhibitors

Source: Reference 26

Sexual health education

Because sexual dysfunction can be caused by underlying psychopathology or physical illness, it is essential to obtain a detailed sexual history at your patient's initial assessment and at every follow-up visit. Patients and providers may be guarded when discussing sexual health, which can be a barrier to providing comprehensive health care. The organizations listed in ***Related Resources*** (***page 34***) can provide information and materials to help patients and health care providers better understand sexual health. Addressing the importance of sexual health in a com-

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Loss of sexual desire in patients taking SSRIs may be the result of reduced mesolimbic dopaminergic activity

SSRIs and sexual dysfunction

Clinical Point

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Related Resources

- American Association of Sexuality Educators, Counselors, and Therapists. www.aasect.org.
- Sexual Medicine and Wellness Center. www.methodistsexualwellness.com.
- The Sexual Health Network. www.sexualhealth.com.
- International Society for the Study of Women's Sexual Health. www.isswsh.org.

Drug Brand Names

Bethanechol • Urecholine
Citalopram • Celexa
Clomipramine • Anafranil
Dapoxetine • Priligy
Digoxin • Lanoxin
Escitalopram • Lexapro
Fluoxetine • Prozac
Fluvoxamine • Luvox
Paroxetine • Paxil
Sertraline • Zoloft
Sildenafil • Viagra

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

prehensive, culturally sensitive manner can substantially improve our patients' medication compliance and prognosis.

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Bottom Line

Selective serotonin reuptake inhibitors (SSRIs) can adversely affect all aspects of the human sexual response cycle. Obtaining a detailed sexual history in a culturally sensitive manner may facilitate early detection and accurate estimation of SSRI-related sexual dysfunction and can prompt interventions to enhance patients' medication compliance and improve their overall prognosis.