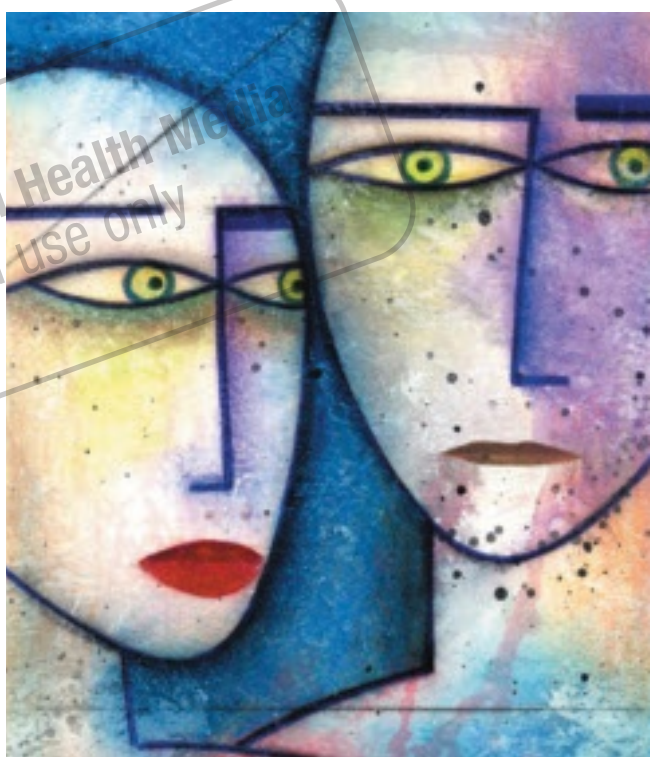
Current PSYCHIATRY

Restoring sexual function: Which medications show benefit?

When trying centrally acting or topical agents, also address patients' psychopathologies

Sexual disorders such as premature ejaculation, erectile dysfunction (ED), and low libido reduce quality of life in patients with depression, anxiety, and other psychiatric illnesses. In addition, sexual dysfunction is a side effect of many drugs used to treat psychiatric disorders.[1]

Psychiatry—with its biopsychosocial model—can easily assume the evaluation and treatment of sexual disorders. To inform your practice, this article provides an update on pharmacotherapy for the 3 most common sexual disorders. Its emphasis on biologic treatment is not intended to minimize the importance of psychological interventions.



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Premature ejaculation

Premature ejaculation is one of the most common male sexual complaints. In some surveys, approximately 30% of men express concern about ejaculating too rapidly.[2] Behavioral therapy often is effective (***Box 1, page 20***), but in my experience most male patients prefer a pharmacologic approach to sexual problems.

Anesthetic creams. Locally applied anesthetic creams—such as prilocaine, lidocaine mixtures, and creams consisting of natural herbs—can increase ejaculatory latency by approximately 7 to 10 minutes. The major side effect of these preparations is penile hypoanesthesia. The man also must use a condom or wash off the cream before vaginal penetration to minimize vaginal absorption.[3]

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The SSRI dose needed to delay ejaculation usually is similar to the dose needed to treat depressive disorders

Box 1

Start-stop technique for premature ejaculation*

1. With male lying on back, partner strokes penis until male signals that ejaculation will occur with continued stimulation†
2. Stroking stops, and erection is allowed to subside, then stroking resumes
3. Repeat steps 1 and 2 four times, 2 times/week
4. Ejaculatory latency will increase
5. Partner assumes female-superior position and moves up and down until male indicates ejaculation is imminent

* Behavioral therapy for heterosexual couples. Oral-genital stimulation can be utilized between steps 4 and 5

† Frenulum squeeze technique is similar except that partner squeezes frenulum of penis at sign of male excitement

Centrally active medications. No medications are FDA-approved for premature ejaculation, but case reports describe the off-label use of monoamine oxidase inhibitors, tricyclic antidepressants, and antipsychotics.[4] The selective serotonin reuptake inhibitors (SSRIs) paroxetine, sertraline, and fluoxetine also delay ejaculation, as shown in double-blind controlled studies.

Among the SSRIs, paroxetine appears to have the greatest effect on ejaculatory latency (***Table 1, page 29***).[5] Most trials have found that the dose needed to delay ejaculation is similar to the dose necessary to treat depressive disorders.

Clomipramine, a tricyclic antidepressant with strong serotonergic activity, has been shown in double-blind trials to be effective in treating rapid ejaculation on an as-needed basis. By contrast, SSRIs appear to require chronic dosing to be effective. Clomipramine usually is taken 4 to 6 hours before coitus in doses of 25 to 50 mg. Low-dose lorazepam (0.5 to 1 mg) taken 30 minutes before coitus also may be effective in some men.[2]

Some case reports suggest that phosphodiesterase type 5 inhibitors (PDE-5 inhibitors) may help to delay ejaculation, but this effect has not been borne out in double-blind studies.[6]

Recommendation. Most psychiatrists can easily provide pharmacotherapy for premature ejaculation because we commonly use the medications in clinical practice. As initial treatment, I recommend trying clomipramine, 25 to 50 mg 4 to 6 hours before coitus. Other authors prefer a trial of paroxetine, 20 mg daily.

Erectile dysfunction

Men with major depressive disorder, anxiety disorders, and psychotic disorders have higher rates of ED, compared with the general male population. ED also can be a side effect of—and adversely affect adherence to—antidepressant and antipsychotic therapy.[7] Restored erectile function can positively affect patients' self-esteem and sense of personal efficacy and may facilitate recovery from depression.[8]

PDE-5 inhibitors. Nitric oxide release triggers the production of cyclic guanosine monophosphate, which leads to decreased intracellular calcium, smooth muscle relaxation, and penile erection. All available PDE-5 inhibitors work by inhibiting the degradation of cyclic guanosine monophosphate. They are highly specific, vary somewhat in selectivity for other phosphodiesterase enzyme types, and differ in duration of action (***Table 2, page 29***).

Common side effects include dyspepsia, stuffy nose, and headache. The use of PDE-5 inhibitors with nitrates is contraindicated because of the risk of severe hypotension. Use PDE-5 inhibitors cautiously:

- with alpha blockers because of the risk of hypotension
- in men with aortic stenosis, recent myocardial infarction, unstable angina, heart failure, arrhythmias, degenerative retinal disease, or poorly controlled hypertension.[9]

Also warn patients about the rare possibility of priapism and to go immediately to the nearest emergency room if an erection lasts >4 hours without sexual stimulation.

Cases of sudden loss of hearing or vision (nonarteritic anterior ischemic optic neuropathy) have been associated with PDE-5 inhibitor use.[10,11] To date, there is insufficient evidence to determine if these adverse events are chance associations in

continued on page 29

continued from page 20

a population at risk for hearing and vision losses from other causes such as aging.

Other options. Other accepted options for treating ED include intracavernosal injection of vasoactive substances such as phentolamine or prostaglandin E1, or intraurethral insertion of prostaglandins.[12] Since the advent of PDE-5 inhibitors, these approaches are rarely used.

Cabergoline. Off-label use of dopaminergic agents such as cabergoline may be moderately effective in treating ED in men who do not respond adequately to PDE-5 inhibitors. Cabergoline is a dopamine D2 receptor agonist used to treat hyperprolactinemia and Parkinson's disease.

In a randomized, double-blind, placebo-controlled study, 402 men who did not respond to sildenafil received cabergoline, 0.5 to 1 mg weekly for 6 months. Among the 370 men (92%) who completed the trial, mean weekly intercourse episodes increased from 1.4 to 2.2, compared with 1.2 to 1.4 in men who received placebo.[13]

Cabergoline also improved erectile function and sexual satisfaction in a randomized, double-blind, placebo-controlled trial of 50 men with psychogenic erectile dysfunction.[14]

Treatment outcomes. Most studies report positive psychological responses to ED reversal in men using PDE-5 inhibitors. Successful therapy has been associated with increased self-esteem, satisfaction, and sexual satisfaction.[8] Some studies have found increased sexual satisfaction in the partner as well.[15]

Approximately 50% of PDE-5 inhibitor prescriptions are not refilled, however, and some case reports suggest that restored erectile function can result in:

- divorce and marital discord
- no change in partner-related activity.[16]

Given the symbolic meaning and interpersonal context of sexual activity, it is not surprising that restored sexual function does not always have a positive psychological outcome. Combined psychological and pharmacologic therapy may improve treatment outcomes in men with ED.[17]

Table 1

Drug treatment options for premature ejaculation

Drug	Dosage	Common side effects
Paroxetine	20 to 40 mg/d	Nausea, headache
Clomipramine	25 to 50 mg 4 to 6 hours before sexual activity	Nausea, fatigue
Lorazepam	0.5 to 1 mg 30 minutes before sexual activity	Sedation

Source: Reference 5

Table 2

Duration of action of PDE-5 inhibitors

Drug	Duration
Sildenafil	4 hours
Vardenafil	4 hours
Tadalafil	24 to 36 hours

PDE-5: phosphodiesterase type 5

Recommendation. Because erectile problems are common in psychiatric patients, most psychiatrists should feel comfortable treating ED with PDE-5 inhibitors. In general, these agents are relatively safe. Reversing drug-induced sexual dysfunction may improve patients' adherence to psychotropics, increase self-esteem, and improve relationships with sexual partners.

Hypoactive sexual desire

PDE-5 inhibitors. The success of PDE-5 inhibitors in treating ED led to investigations into whether these agents also could treat female sexual disorders. Large multisite trials using sildenafil failed to find evidence of efficacy in treating female hypoactive sexual desire or arousal disorders, however.[18] Similarly, trials of topical prostaglandin E1 and alpha blockers were unsuccessful in women.

Some small studies suggested that PDE-5 inhibitors might be useful in:

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PDE-5 inhibitors are relatively safe and effective for ED, but approximately 50% of prescriptions are not refilled

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Bupropion may increase orgasm completion and other sexual responses in women with low sexual desire disorders

Box 2

Testosterone for female hypoactive sexual desire?

Transdermal testosterone can increase sexual desire in surgically menopausal women—according to numerous large, multisite, double-blind studies[23]—and has been approved for this indication in the European Union. Testosterone also has been reported to increase sexual desire in women who experienced natural menopause and in normal premenopausal women.[24]

In the United States, testosterone is not FDA-approved for treating low sexual desire. Considerable off-label use occurs, although long-term safety is unknown.

Various factors complicate the study of testosterone's relationship to female libido:

- 3 large population studies have found minimal evidence of a relationship between endogenous androgenic activity and measures of female sexual responsiveness; these results may reflect an absence of such a relationship or methodologic weaknesses.
- The sensitivity and specificity of available assays to detect testosterone in women are seriously limited.
- Much of the active testosterone in the female body is made by intracellular conversion or testosterone precursors and thus may not be detected by assays of serum androgen levels.[24]

- women with normal libido but decreased arousal[19]
- young women with normal libido and inability to reach orgasm.[20]

These studies used small sample sizes and have not been replicated, however.

Testosterone therapy. In the 1940s, case reports suggested increased libido as a side effect when women were treated with androgens for metastatic cancer. In a prospective study, Sherwin and Gelfand[21] found increased sexual desire, sexual arousal, and rates of coitus and orgasm in women injected with testosterone/estrogen preparations after surgical menopausal.

More recently, Shifren et al[22] showed in a randomized, placebo-controlled trial that transdermal testosterone, 150 or 300 micrograms/day for 12 weeks, improved sexual function and psychological well-being in women age 31 to 56 after surgical menopause. Since then, numerous large, multisite, double-blind studies have demonstrated the efficacy of transdermal testosterone in treating low sexual desire in surgically menopausal women.[23] Transdermal testosterone has been approved for this indication in the European Union but not in the United States.

Testosterone also has been reported to increase sexual desire in women who experienced natural menopause and in normal premenopausal women.[24] The study of the relationship of testosterone to libido in women is complicated by numerous factors, however (***Box 2***).[23,24]

Other agents. Recent research has focused on centrally active compounds' effect on libido. One agent in development is flibanserin, a serotonergic 5HT2 antagonist and a 5HT1a agonist. Data from large, multisite studies indicates that this compound increases libido in women with low sexual desire.

Some evidence suggests that bupropion—which has noradrenergic and dopaminergic agonist properties—increases orgasm completion and other measures of sexual responsiveness in women with hypoactive sexual desire disorders.[25]

The investigational compound bremelanotide—a synthetic version of melanocytes stimulating hormone—is administered intranasally and appears to acutely influence libido in women.[26] Trials have been delayed because of this agent's effects on blood pressure.

Herbal compounds. Some herbal compounds are being sold for low-desire

continued on page 35

For more on sexual disorders

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MAY 2004

continued from page 30

complaints. Web sites for 2 herbal compounds, Ziti and Alibi, cite unpublished double-blind studies attesting to their efficacy. Because these studies are unpublished, one cannot evaluate their methodologies.

One double-blind study of the herbal compound ArginMax—which contains ginseng, ginkgo, damiana, L-arginine, and multivitamins—suggests efficacy in a small group of women with poorly specified sexual problems.[27] Zestra, a topical herbal compound, has been evaluated in large multisite studies and found to be effective in increasing female sexual responsiveness.[28]

Other approaches. Some clinicians advocate using the testosterone precursor dehydroepiandrosterone (DHEA) for low sexual desire, although evidence does not support its efficacy.[29]

A battery-operated device is FDA-approved for treating sexual dysfunction in women. The clitoral vacuum increases vaginal engorgement and various indices of sexual responsiveness. This device's target population is not clearly defined.[30]

Recommendation. The first step in treating hypoactive sexual desire disorder is to identify causes that can be treated. Low libido is common in patients with anxiety and depressive disorders and may remit with successful treatment of these primary difficulties.

When medication side effects are causing hypoactive sexual desire, consider substituting another drug or using antidotes such as buspirone or bupropion. Unfortunately, however, most sexual desire problems are idiopathic.

Testosterone therapy has been shown to improve libido, although it is not FDA-approved for this indication. Considerable off-label use occurs, but long-term safety is unknown.

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Sexual disorders

Clinical Point

Hypoactive sexual desire may remit with successful treatment of a primary anxiety or depressive disorder

Related Resource

- Medline Plus. Sexual problems overview. www.nlm.nih.gov/medlineplus/ency/article/001951.htm.

Drug Brand Names

Bupropion • Wellbutrin
Buspirone • BuSpar
Cabergoline • Dostinex
Clomipramine • Anafranil
Fluoxetine • Prozac
Lorazepam • Ativan
Paroxetine • Paxil
Phentolamine • Regitine
Prostaglandin E1 • Liprostin
Sertraline • Zoloft
Sildenafil • Viagr
Tadalafil • Cialis
Vardenafil • Levitra

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Bottom Line

For initial pharmacologic treatment of premature ejaculation, consider clomipramine, 25 to 50 mg taken 4 to 6 hours before coitus, or paroxetine, 20 mg taken daily. Phosphodiesterase type 5 inhibitors are relatively safe for treating erectile dysfunction (ED) and may be useful for managing medication-related ED. Few options exist for female hypoactive sexual desire, so start by treating any primary anxiety or depression.