

How Psychiatrists Can Build New Therapies for Impotence

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Issue: *Impotence is a common and distressful condition in men.*

Psychiatrists are uniquely positioned to treat male sexual dysfunction of both functional and organic etiologies by combining traditional psychological approaches with a variety of new therapeutic agents.

Impotence, the inability to maintain an erection sufficient for intercourse, is more properly called *erectile dysfunction*.¹ Up to 20 million men in the United States have this problem to some degree.² The multiple causes of erectile dysfunction include vascular insufficiency, neurologic causes, endocrine pathology (reproductive hormones, thyroid, diabetes), drugs, local pathology in the penis, and psychological/psychiatric problems.¹

Plumbing and Listening Are the Traditional Treatment Strategies

Until recently, effective treatment of organic causes of erectile dysfunction was often elusive and usually involved a urologic approach, such as prostheses and implants to compensate for faulty wires and leaky plumbing. This surgical strategy bypasses diseased peripheral nerves and inadequate vascular supply to create erections mechanically and on demand, but has serious limitations in terms of patient and partner acceptability.^{1,3}

In men who have a functional etiology to their erectile dysfunction, the treatment strategy takes a psychiatric approach, namely, attention to partners and functional disorders, appropriate use or nonuse of psychotropic (as well as nonpsychotropic) drugs, managing problems of self-esteem,

and supervising appropriate lifestyle changes.¹⁻³ Although often effective in cases of true functional etiology, psychiatric approaches have proved seriously limited in the much more common situation in which the cause of erectile dysfunction is multifactorial. Typically, some combination of alcohol, diabetes, smoking, hypertension, and antihypertensive or psychotropic drugs may create or magnify partner problems, produce performance anxiety, and cause a detumescent downward spiral of male sexual dysfunction.¹⁻³

Dopamine: The Good-for-Sex Neurotransmitter

The physiology of the male sexual response starts in the CNS. Libido, arousal, and pleasure seem to be mediated in the mesolimbic "pleasure center," which utilizes dopamine as the pleasure neurotransmitter. Boosting dopamine may enhance sexual response, whereas blocking it may compromise sexual response.⁴ Thus, pro-dopaminergic agents such as bupropion, methylphenidate, and amphetamine may be good for sex, and dopamine receptor blocking antipsychotics may be bad for sex.⁴

Serotonin: The Bad-for-Sex Neurotransmitter

Serotonin seems to be a spoilsport in terms of the sexual response, possi-

bly at 2 levels in the CNS. First, serotonin may diminish the release of pleasurable dopamine in the mesolimbic pleasure center.⁴ Second, serotonin, via a serotonin-2 receptor, may block the ejaculatory and orgasmic response at the level of spinal reflex centers that innervate the penis with sympathetic and parasympathetic nerves.⁴ Thus, agents that boost serotonin (such as serotonin selective reuptake inhibitors) can be bad for sex, whereas agents that block serotonin-2 receptors (such as nefazodone and mirtazapine) fail to produce these sexual problems.⁴

Prostaglandin: A Painful Alternative

Smooth muscle relaxation is now known to be the key element to attaining an erection. Administration of prostaglandins can relax penile smooth muscle and elicit erections in a manner that mimics typical physiologic mechanisms.⁵ Thus,

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intracavernous injection of the prostaglandin alprostadil produces erections not only in men with organic causes of impotence, but also in men with functional causes, and even in the common situation of multifactorial causes.⁵ Limitations of this somewhat masochistic approach include unacceptability of self-injection, lack of spontaneity, and the possibility of too much of a good thing, namely a prolonged and painful erection called priapism.

Yes, There Is NO Neurotransmitter in the Penis

In last month's BRAINSTORMS, nitric oxide (NO) was shown to be a CNS neurotransmitter. But it is more. NO also functions as the neurotransmitter that relaxes smooth muscle in the penis to cause a physiologic erection during normal male sexual response by stimulating guanylyl cyclase to manufacture cGMP. It is this cGMP which then relaxes the penile smooth muscle and produces a physiologic erection.^{1,3,6}

Once cGMP is destroyed by phosphodiesterase, the penis detumesces. This observation led to the proposal that if cGMP could somehow be enhanced, perhaps so could physiologic erections. In fact, the novel drug sildenafil (Viagra), about to be released by the FDA, works in this very manner.⁷⁻⁹

Anti-Phosphodiesterase Revival

The strategy of phosphodiesterase inhibition has three potential advantages⁷⁻⁹: it allows oral administration; it leads to erections during physiologic sexual arousal (not requiring on-demand mechanics); and it boosts the most common type of problem, namely partial, intermittent erectile dysfunction of multifactorial causation.

Take-Home Points

- ◆ The physiologic mechanisms of male sexual functioning, including erection and ejaculation, are being rapidly clarified
- ◆ Traditional psychiatric approaches to male sexual dysfunction are attention to partners and functional disorders and appropriate use or nonuse of psychotropic drugs
- ◆ Traditional psychiatric and surgical treatments can now be powerfully augmented by administering prostaglandins and soon neurotransmitter-specific approaches, such as novel oral phosphodiesterase inhibitors, will be available

First, penile phosphodiesterase is a specific subtype that is not present in all tissues. Thus, selectively targeting this enzyme leads to tissue selective phosphodiesterase inhibition. The value of this selectivity is better systemic tolerability even if the drug is taken orally. Second, since cGMP mediates physiologic erections, increasing cGMP during sexual arousal enhances the erection, creating for most men a much more natural and spontaneous experience than mechanical manipulation. Finally, sexual arousal previously insufficient to cause an erection may now do so; arteries too clogged with cholesterol from atherosclerosis, smoking, and diabetes to create a robust erection may now enable an erection; nerves too sick from diabetes or surgery (or even poorly fitting bicycle seats) may now work well enough so that an erection can occur.

A Neurotransmitter-Based Approach to Erectile Dysfunction

As new treatments based on neurotransmitter pharmacology continue to evolve, the psychiatrist is increasingly taking a central role in managing male

sexual dysfunction, including erectile dysfunction. Future therapies on the horizon are also based on neurotransmitter pharmacology and include a dopamine agonist (apomorphine), an α -adrenergic antagonist (phentolamine), and the neurotransmitter vasoactive intestinal peptide. Hopefully, setting up treatment programs for male sexual dysfunction will expand the practice opportunities for psychiatrists and erect new therapies for impotence for millions of men suffering from this problem.

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— Coming in March —
a pictorial description of
nitric oxide physiology
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