

COVER STORY: TRI-POINT SERIES

From The Endocrine Society's Research Affairs Committee
Co-edited by Steven Grinspoon, M.D., and Ellen Seely, M.D.

2 PERSPECTIVES ON THE ETIOLOGY AND TREATMENT OF ERECTILE DYSFUNCTION

A MATTER OF THE HEART AND THE BRAIN?

BY JONATHAN P. JARROW, M.D., & BRADLEY D. AMAWALT, M.D.

Erectile dysfunction is a common disorder that was originally thought to be largely “psychogenic.” However, there is generally a physical cause for erectile dysfunction. The effectiveness of oral type 5 phosphodiesterase inhibitors as treatments for erectile dysfunction has highlighted the importance of vascular function in penile tumescence. Recent data demonstrate that hormones and brain neurotransmitters are important for normal erectile function.



Giving the urologist's perspective is Dr. Jarrow, Professor of Urology, Radiology, Pathology, and Reproductive Medicine at Johns Hopkins Medical Institutions.

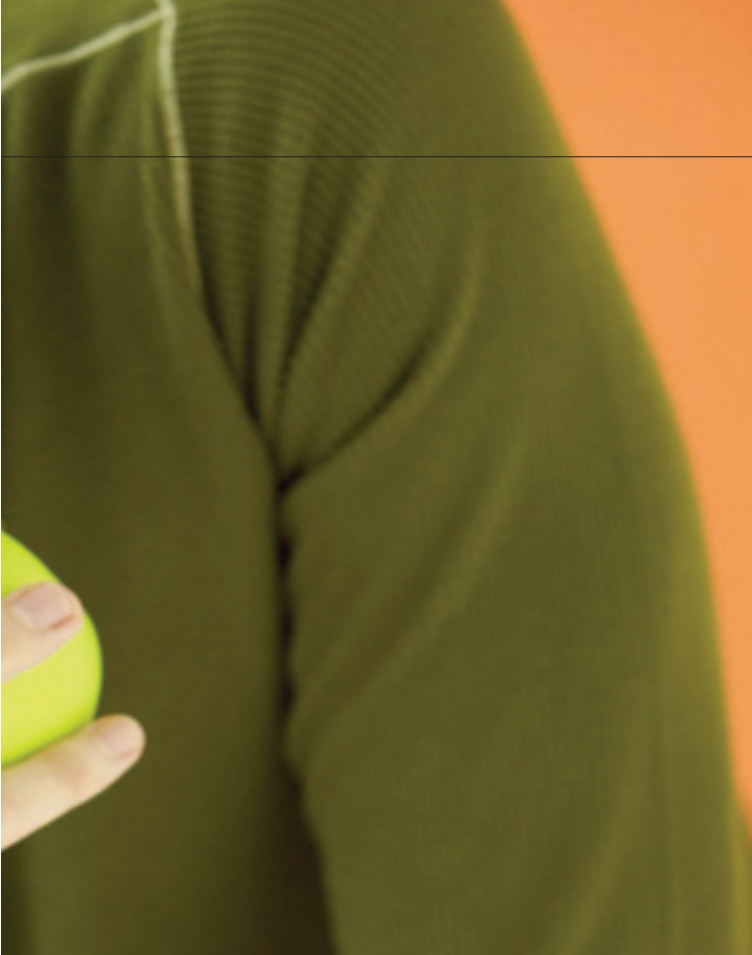
Giving the endocrinologist's perspective is Dr. Anawalt, Associate Professor of Medicine and Endocrinology at Virginia Puget Sound Health Science Center.

Anatomy and Physiology of Erectile Dysfunction

Erectile dysfunction is an extremely common disorder that is just one of many male sexual complaints. Other male sexual function disorders include premature ejaculation (the most common sexual complaint), reduced libido, and anorgasmia. The best epidemiological data suggest that 1 in 3 adult men suffer from some degree of erectile dysfunction.¹ The prevalence and severity of erectile dysfunction increases with age, although there is no age at which it is “normal” to have erectile dysfunction.

Normal Process

Erectile function requires a normal endocrine milieu, intact innervations of the corpora, adequate arterial blood flow, and compliance of the sinusoidal tissue. The first response to stimulation of an erection, by either direct tactile stimulation (reflexogenic) or mental stimulation (psychogenic), is smooth muscle relaxation of the penile arteries and the sinusoidal tissue. The vascular smooth muscle relaxation causes a decrease in the vascular resistance within the corpora and an influx of blood. Detumescence, or loss of an erection, normally occurs with ejaculation through adrenergic discharge that causes vascular smooth muscle contraction and thus a decrease in arterial inflow.² This same mechanism comes into play with psychogenic erectile dysfunction due to performance anxiety



associated with increased catecholamine release from the adrenal medulla.

Molecular Mechanisms

The molecular mechanism of an erection involves multiple pathways, but the primary one is believed to be the nitric oxide–cyclic guanosine (cGMP) pathway. Nitric oxide (NO) is produced from L-arginine catalyzed by the enzyme nitric oxide synthase (NOS). Nitric oxide goes into the smooth muscle cells and binds to guanylate cyclase, which catalyses the production of cGMP from guanosine triphosphate (GTP).³ Phosphodiesterase enzyme type 5 (PDE-5) within the smooth muscle cell metabolizes cGMP into 5'GMP, which inhibits an erection. The currently available oral agents used in treating erectile dysfunction work by selectively inhibiting PDE-5. Thus, they prevent the breakdown of cGMP and amplify any signals that reach the penis.

From the Urologist

Therapeutic Options for Erectile Dysfunction:

- Sex therapy
- Endocrine therapy
- Oral PDE-5 inhibitors
- Intra-penile drugs
- External devices
- Implantable devices
- Vascular surgery

Vasodilator Therapy for Erectile Dysfunction

Therapeutic options for erectile dysfunction include sex therapy, hormonal therapy, oral medications, penile medications, and devices, both external and surgically implantable (Table 1). There are three FDA-approved medications indicated for the treatment of erectile dysfunction and they are effective in approximately 70% of un-selected erectile dysfunction patients. All three agents work via PDE-5 inhibition. The efficacy and side effect profile of these medications is quite similar.⁴ The vast majority of patients have a similar response to each medication, although some prefer one over the others. The major difference in the medications is pharmacokinetic, some having a longer half-life than others. The adverse effects are minimal and include facial flushing, headaches, indigestion, and visual disturbance. These medications are contraindicated in patients who have access to, or are taking, nitrate medications. In addition, patients in whom sexual activity is not advisable due to cardiovascular disease should not be treated with oral agents or any other therapy for erectile dysfunction.

An alternative approach if the oral agents are not effective or are contraindicated is administration of vasodilators directly to the penis. The most commonly used medication is alprostadil or PGE₁. It can be given as a single agent or combined with two other vasodilators—papaverine and phentolamine. Side effects include penile pain, infection, bruising, and priapism. Many patients who are initially reluctant to perform self-injection therapy find it quite acceptable after experiencing a test injection; however, the long-term drop out rate is quite high—about 45%.⁵

Alternative Therapies

Various devices are available to treat erectile dysfunction. These include the non-surgical external vacuum erection device and the surgically implanted penile prostheses. The vacuum device is highly effective and economical. It does not produce a normal or natural erection, however, and thus patient and partner acceptability is only about 50%. In contrast, the penile implant has the highest patient and partner satisfaction rate, approaching 90%. There are a variety of devices available today, including simple malleable rods and inflatable cylinders. The main risks of penile prosthetics are infection, erosion, and mechanical failure. The advantages of the malleable rods are that they are simple to insert and have a low mechanical failure rate. The inflatable prosthetics give a much better cosmetic result but have a higher rate of mechanical failure, approximately 15% in the first 10 years.

Vascular surgery, including occlusion of venous outflow and arterial reconstruction, has been used in select patients with vascular pathology. However, the risk–benefit ratio does not support the clinical use of the venous ligation procedure. Arterial reconstructive surgery has been shown to be effective in young healthy patients with segmental arterial occlusion due to trauma; however, this is an extremely rare patient.⁶

Urologists' Role in Treatment of Erectile Dysfunction

Urology, with only a few exceptions, was once the primary specialty to manage patients with erectile dysfunction. Since the approval of effective oral agents for treating this disorder, the vast majority of patients with erectile dysfunction are initially managed by primary care physicians. The current indications for urological referral include patients who have 1) failed medical therapy, 2) signs or symptoms of Peyronie's disease, 3) a history of priapism or trauma, or 4) primary erectile dysfunction. Although the currently available oral agents are highly effective, they do not work for all patients and, as mentioned above, a variety of effective alternatives are available to patients who desire to be sexually active.

Neuropsychocrinology of Erectile Function

Brain hormones and central nervous system neurotransmitters play a primary role in normal penile erections. Perturbations of these hormones and neurotransmitters commonly cause sexual and erectile dysfunction.

Sex Steroid Hormones and Erectile Function

Testosterone is necessary for normal libido and for quantitatively and qualitatively normal erections. Animal and human studies indicate that testosterone facilitates (directly or via its metabolites) normal penile vasodilation and tumescence in response to sexual stimuli.¹⁻³ In addition, testosterone may synchronize the central nervous system and penile response to sexual stimuli. Animal studies indicate that testosterone is important for timely initiation and cessation of erections by stimulating expression of nitric oxide synthase and phosphodiesterase 5 gene expression.⁴ The effects of testosterone on sexual function appear to differ in younger and older men. Younger men with experimentally manipulated serum testosterone levels maintain relatively normal sexual and spontaneous erectile function with circulating testosterone levels that are 30%–50% of the lower limit of normal, and sexual function does not change significantly with increasing dosages of testosterone.⁵ Older men with experimentally manipulated serum testosterone levels appear to require at least normal serum free testosterone

levels for normal baseline sexual function, and they experience a dosage-dependent increase above baseline in waking and spontaneous erections and libido with testosterone dosages up to 3–5 times typical physiological replacement dosages.⁶ In addition, testosterone appears to facilitate maximal tumescence, an observation with clinical significance in men with erectile dysfunction and low serum testosterone levels. Small human clinical trials have shown that exogenous testosterone therapy augments the tumescent effects of oral phosphodiesterase inhibitors in the treatment of men with erectile dysfunction and low or low-normal serum testosterone levels.⁷

Prolactin, Melanocortin, and Erectile Function

Brain hormones such as prolactin and melanocortin modulate sexual and erectile function. Prolactin tends to inhibit sexual and erectile function, and some investigators have proposed that post-orgasm elevations in prolactin induce sexual satiety and refractoriness to sexual desire and erections.⁸ The mechanisms of prolactin-induced inhibition of male sexual function include suppression of pituitary gonadotropins and suppression of central nervous system dopaminergic pathways. In addition, at supraphysiological levels, prolactin may directly inhibit penile vasodilation. Epidemiological studies have shown decreased sexual and erectile function in men treated with anti-psychotic drugs that raise prolactin levels; men treated with anti-psychotic drugs that are not associated with hyperprolactinemia have significantly less sexual dysfunction. Because mild hyperprolactinemia is common in men with erection dysfunction, it is tempting to speculate that dopamine agonists might be beneficial in men with sexual dysfunction and hyperprolactinemia. However, carefully designed, placebo-controlled trials must be done to prove this concept before clinicians should consider dopamine agonists for this indication.

Melanocortins are peptides derived from proopiomelanocortin (POMC) and are widely expressed in the central nervous system and in various peripheral tissues. Melanocortins inhibit appetite and stimulate sexual behavior via the melanocortin-4 receptor. Studies of rats have shown that a melanocyte-stimulating hormone induces erections, and recent studies have shown that a non-selective melanocortin receptor agonist (PT-141) stimulates erections in normal men. PT-141 also potentiates the effects of a phosphodiesterase inhibitor on penile tumescence in men with erectile dysfunction.^{9, 10} Melanocortin agonists are a promising novel class of drugs for treatment of male sexual and erectile dysfunction.

Central Neurotransmitters and Erectile Function

Central neurotransmitters—such as dopamine, noradrenaline, and serotonin—modulate sexual and erectile function. Animal studies have shown that dopamine and noradrenaline acutely stimulate male sexual function.^{11, 12} Serotonin generally inhibits erections, although stimulat-

From the Endocrinologist

Treatment Options:

- Testosterone facilitates penile vasodilation and tumescence by increasing nitric oxide synthase activity.
- Dopamine and noradrenaline stimulate normal male sexual function and erections.
- Serotonin generally inhibits normal male sexual function and erections.
- Melanocortin is a new therapy that could be useful for treating erectile dysfunction.

ing certain 5-hydroxytryptamine receptors may increase erections.¹² In humans, serotonergic antidepressants (e.g., paroxetine, fluoxetine, citalopram, and sertraline) are associated with erectile dysfunction in up to 30% of men, but dopaminergic and noradrenergic antidepressants (e.g., bupropion) or selective 5_{a1} hydroxytryptamine agonists (e.g., mirtazepine) cause less erectile dysfunction and might even enhance erectile function.¹³ The mechanisms of erectile dysfunction due to serotonergic antidepressants include inhibition of brain signals to the penis, serotonin-induced hyperprolactinemia, and perhaps inhibition of penile nitric oxide synthase.

The Endocrinologist's Role in Treatment of Erectile Dysfunction

The endocrinologist could be involved in the initial evaluation of patients with erectile dysfunction or of patients refractory to phosphodiesterase inhibitors. The clinician should carefully evaluate for clinical and biochemical evidence of hypogonadism (i.e., low calculated free and weakly bound serum testosterone). A clinical trial of testosterone replacement should be considered for men with erectile dysfunction and low serum testosterone levels. Men with erec-

tile dysfunction and low serum testosterone rarely respond to testosterone monotherapy, but the combination of exogenous testosterone plus a penile vasodilator such as an oral phosphodiesterase may be synergistic. If possible, the endocrinologist should also discontinue medications that raise brain serotonin or serum prolactin levels. In the future, there could be new neuroendocrine therapies for erectile dysfunction, such as selective melanocortin agonists. ■

REFERENCES

Urologist Article

1. Feldman HA, Goldstein I, Hatzichristou, DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *J Urol*, 1994;151:54–61.
2. Bosch RJ, Benard F, Aboseif SR, Stief CG, Lue TF, Tanagho EA. Penile detumescence: characterization of three phases. *J Urol*, 1991;146:867–871.
3. Trigo-Rocha F, Aronson WJ, Hohenfellner M, Ignarro LJ, Rajfer J, Lue TF. Nitric oxide and cGMP: mediators of pelvic nerve-stimulated erection in dogs. *Am J Physiol*, 1993;264(2 Pt 2):H419–H422.
4. Montague DK, Jarow JP, Broderick GA, et al. Chapter 1: The management of erectile dysfunction: an AUA update. *J Urol*, 2005; 174:230–239.
5. Sexton WJ, Benedict JF, Jarow JP. Comparison of long-term outcomes of penile prostheses and intracavernosal injection therapy. *J Urol*, 1998;159:811–815.
6. Jarow JP, DeFranzo AJ. Long-term results of arterial bypass surgery for impotence secondary to segmental vascular disease. *J Urol*, 1996;156:982–985.

Endocrinologist Article

1. Bancroft J. The endocrinology of sexual arousal. *J Endocrinol*, 2005;186:411–427.
2. Zhang Xh, Morrelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. *Eur Urol*, 2005;174:657–658.
3. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol (Oxf)*, 2003; 58:632–638.
4. Vignozzi L, Corona G, Petrone L, et al. Testosterone and sexual activity. *J Endocrinol Invest*, 2005;28:39–44.
5. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab*, 2001;281:1172–1181.
6. Gray PB, Singh Ab, Woodhouse LJ, et al. Dose-dependent effects of testosterone on sexual function, mood and visuospatial cognition in older men. *J Clin Endocrinol Metab*, 2005;90:3838–3846.
7. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol*, 2004;172:658–663.
8. Krüger THC, Haake P, Hartmann U, Schedlowski M, Exton MS. Orgasm-induced prolactin secretion: feedback control of sexual drive? *Neurosci Biobehav Rev*, 2002; 26:31–44.
9. Giuliano F. Control of penile erection by the melanocortinergic system: experimental evidences and therapeutic perspectives. *J Androl*, 2004;25:683–691.
10. Wessells H, Blevins JE, Vanderah TW. Melanocortinergic control of penile erection. *Peptides*, 2005;26:1972–1977.
11. Giuliano F and Rampin O. Neural control of erection. *Physiol Behav*, 2004;83:189–201.
12. Hull EM, Muschamp JW, Sato S. Dopamine and serotonin influences on male sexual behavior. *Physiol Behav*, 2004;83:291–307.
13. Labbate LA, Croft HA, Oleshansky MA. Antidepressant-related erectile dysfunction: management via avoidance, switching antidepressants, antidotes, and adaptation. *J Clin Psychiatry*, 2003; 64 Suppl 10:11–19.

About the Tri-Point Series*

This is the eighth appearance of the tri-point perspective articles in *Endocrine News*. Past topics have been:

- Obesity
- Polycystic Ovary Syndrome
- Diabetes
- Androgen Therapy for Women
- Cardiovascular Disease
- Vitamin D's Role as a Hormone
- Thyroid Cancer

The topics, authors, and outside reviewers are selected by The Endocrine Society's Research Affairs Committee (RAC) to explore subject areas from three different angles—that of the basic researcher, the clinical researcher, and the physician-in-practice. The authors write their articles independently. The drafts are then reviewed by contributing co-editors and by independent experts in the specific topic area.

Endocrine News staff would like to thank the efforts of Dr. Steven Grinspoon, RAC Co-Chair, and Dr. Ellen Seely, Co-Editor, for their dedication in developing this series for our readers.

If you have any comments about this feature, please email EndocrineNews@endo-society.org. If you wish to submit a letter to the editor, write to ENLetters@endo-society.org. Letters should not exceed 200 words and, if published, may be edited for length and clarity.

* Archived issues of the Tri-Point series can be found on the *Endocrine News* Web site, www.endo-society.org/news/endocrine_news.