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Hypogonadism and erectile dysfunction: the role for testosterone therapy

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The role of low testosterone levels in erectile dysfunction (ED) remains unclear. Both organic and psychogenic factors contribute to ED, with vasculogenic causes being the most common etiology. Approximately 10–20% of patients with ED are diagnosed with hormonal abnormalities. At the physiologic level, two second messenger systems are involved in mediating erections, one involving cyclic adenosine monophosphate (cAMP) and the other involving cyclic guanosine monophosphate (cGMP). PDE5 inhibitors such as sildenafil promote the cGMP pathway, while alprostadil affects the cAMP pathway. Evidence is strong that, in animal systems, testosterone has direct effects on erectile tissue. However, although testosterone clearly has an impact on libido in humans, its effect on penile function is less clear. Evaluation of ED includes medical, sexual, and psychosocial history assessments, as well as laboratory tests to check for diabetes and hormonal abnormalities. Initial interventions should involve correction of potentially reversible causes of ED, such as hypogonadism. First-line therapy for other patients is typically oral PDE5 inhibitors, such as sildenafil, tadalafil, or vardenafil. For patients who fail treatment with PDE5 inhibitors, local therapies such as intracavernous alprostadil are highly successful. Recent data also support the success of combination therapy with sildenafil and testosterone. This opens the possibility of other combinations of testosterone and other treatments of ED. The ability to exploit multiple pathways in the physiologic processes leading to erection may help improve therapy for ED.
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Introduction

The role that low testosterone levels play in erectile dysfunction (ED) remains unclear. Although both hypogonadism and ED increase with age,[1] serum testosterone levels are similar in patients with ED and in those without, and levels can be similar among patients with different severities of ED.[2,3] These data suggest that ED and hypogonadism may be independent. However, it is possible that a certain threshold level of testosterone is required for full sexual function, and that assessments of mean values may obscure the importance of testosterone in ED. Testosterone supplementation is clearly indicated in hypogonadal patients and may also be of use in other patients with ED and hypogonadal symptoms. Combination therapy with testosterone and other pharmaceutical agents used to treat ED may help patients who are refractory to monotherapy. These findings may be of particular relevance to the patients who do not have a satisfactory response to sildenafil therapy at conventional doses.[4,5]

Epidemiology and etiology of ED

ED affects approximately 30% of men in the US.[6] Prevalence increases with age, with complete ED tripling from 5% in men 40 y of age to 15% in men 70 y of age.[7] Major risk factors for ED include cardiovascular disease, diabetes, depression, and smoking.[8] Psychogenic components play an important role in some patients, but organic causes account for 70–85% of cases.[9,10] For many patients, both psychogenic and organic factors are involved. Organic causes are often classified into four groups: neurogenic, vasculogenic, hormonal, and anatomic (Table 1).[11] The prevalence of these causes depends upon the exact study and the study population being examined. In a retrospective study, vasculogenic causes accounted for 72% of cases in men under the age of 40, while neurogenic causes

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Table 1 Organic causes of erectile dysfunction[11]

Classification	*Description*	*Common causes*
Neurogenic	Disorder of autonomic pelvic nerve stimulation and/or corporal nerve release of endogenous neurotransmitter substances	Diabetes, spinal cord disorders, other neuropathies (eg, parkinsonism or alcohol abuse)
Vasculogenic	Failure to fill the corpora cavernosa due to impairment of arterial inflow and corporal blood pressure (arteriogenic) and/or failure to store blood in the corpora cavernosa because of excessive corporal venous outflow (venogenic)	Atherosclerosis, aging, atherosclerosis risk factors (eg, smoking, hyperlipidemia, corporal fibrosis)
Hormonal	Inadequate production of androgens involved in sexual function	Primary and secondary hypogonadism, hyperprolactinemia, thyroid dysfunction
Anatomic (end-organ)	Presence of traumatic injuries or penile disorders that interfere with sexual function	Peyronie's disease, priapism with resulting fibrosis

accounted for 12%.[10] Other studies have suggested that 10–20% of ED cases may involve hormonal abnormalities.[12,13] Additional factors, such as prescription medications, may also contribute to ED.[11]

Mediators of erection and pharmacologic intervention

The physiologic events involved in the erectile process are now fairly well understood, although some gaps in our knowledge still remain. Stimuli from the brain (psychogenic erection) or direct stimulation of the genitalia (reflexogenic erection) can trigger penile erection. For psychogenic stimuli, sensory information reaches the spine via visual, auditory, tactile, and olfactory sensory afferents in addition to cortical fantasies (Figure 1).[14] The nonadrenergic, noncholinergic nerves promote the release of relaxing substances, primarily nitric oxide, from the nerve endings and the endothelium of the sinusoidal spaces of the corpora cavernosa. Second messenger systems translate this neurotransmitter input into smooth muscle relaxation through two distinct pathways: adenylate cyclase-cyclic adenosine monophosphate (cAMP) and guanylate cyclase-cyclic guanosine monophosphate (cGMP). Nitric oxide stimulates the formation of cGMP, while other messengers, such as prostaglandin E_1, result in increased formation of cAMP. Subsequent phosphorylation of cellular membrane proteins by these molecules results in an efflux of calcium, which leads to vasodilation of the penile arteries and the sinusoidal spaces and erection (Figure 1).[14]

Our growing understanding of the chemical mediators involved in erections has allowed the development of pharmacologic agents that promote pathways leading to erection. Sildenafil, tadalafil, and vardenafil inhibit phosphodiesterase type 5, which breaks down cGMP (Figure 1), resulting in higher levels of cGMP. Another agent that is used to treat ED, alprostadil (prostaglandin E_1), increases the formation of cAMP.[14] Additional compounds that affect these pathways are being actively studied for a potential role in ED therapy.

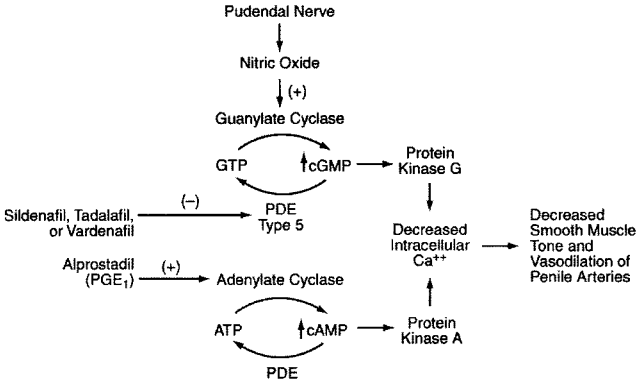

Figure 1 Mediators and pathways involved in penile erection, and mechanism of action of two common therapies for ED, sildenafil, and alprostadil. Adapted with permission from Manecke and Mulhall.[14] GTP indicates guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PDE, phosphodiesterase; ATP, adenosine triphosphate; and cAMP, cyclic adenosine monophosphate.

The role of testosterone reflects a gap in our knowledge of the events leading to penile erection. In humans, testosterone therapy appears to have more significant effects on libido than on erectile capacity.[15,16] The uncertainty of the impact of testosterone on ED is caused by the observations that some severely hypogonadal men continue to have an erectile response[17] and that testosterone replacement in hypogonadal men with ED results in improvement in only 40–60% of patients.[18,19] These findings suggest that testosterone may not make a major contribution to human penile erection. However, in animal studies, testosterone has been shown to support erectile function through a direct effect on the erectile tissue. Experimental castration results in an impaired erectile response,

and testosterone replacement reverses this deficiency. At the cellular level, castration of the rat penis causes apoptosis (programmed cell death), while testosterone replacement results in new DNA synthesis.[20] Both nitric oxide-dependent and nitric oxide-independent pathways have been implicated in erectile responses to testosterone in animals.[17] Furthermore, improvements in sexual function have been observed in hypogonadal men with ED who received testosterone replacement therapy.[21,22] These studies support a role for testosterone in the physiologic processes leading to erection.

Evaluation and first-line therapy for ED

According to the *Recommendations of the First International Consultation on Erectile Dysfunction*, which was sponsored in 1999 by the World Health Organization and other leading organizations in the fields of health and sexual dysfunction, all patients being evaluated for ED should undergo comprehensive medical, sexual, and psychosocial history evaluations, including assessments of ED intensity and impact.[23]

Recommended diagnostic tests include fasting glucose or glycosylated hemoglobin and lipid profile to rule out diabetes and hyperlipidemia, and evaluation of the hypothalamic–pituitary–gonadal axis with a testosterone assay. Other serum assays, including serum prolactin and luteinizing hormone, and additional examinations, such as psychiatric evaluations, should be employed as needed.[23]

In some cases, ED may be alleviated by alterations in lifestyle, such as cessation of smoking and substance abuse, psychosocial counseling, and changes in prescription or nonprescription medications (Figure 2).[23] For hypogonadal patients, testosterone replacement therapy may also improve ED.[23] For the majority of patients who do not respond to or who are not candidates for such interventions, the oral agents sildenafil, tadalafil, or vardenafil are the most frequent choice for first-line therapy. However, in one study, intracavernous injection therapy with alprostadil (either alone or in combination with papaverine and phentolamine) was preferred by 33% of patients who responded to monotherapy with either sildenafil or intracavernous agents.[24]

Treating oral therapy failures: evidence for new options

Although sildenafil is highly effective in the treatment of both organic and psychogenic ED, approximately 30–40% of patients do not have a satisfactory response to therapy.[4,5] For these patients, local

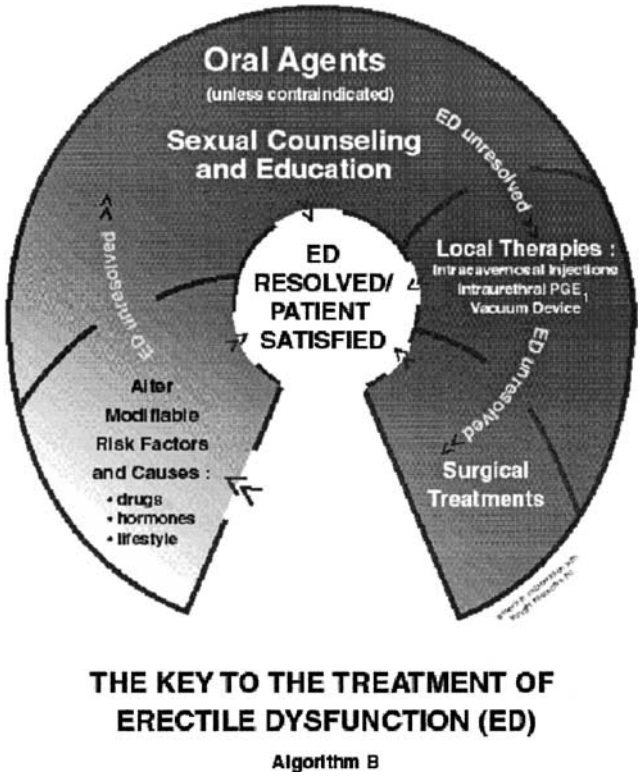

Figure 2 Treatment algorithm for ED.[23] Combination therapies may be utilized as a second-line treatment. Adapted with permission from Jardin *et al.*[23]

therapies, such as intracavernous alprostadil, intraurethral alprostadil, or vacuum devices, represent the next line of therapy (Figure 2).[23] Recent studies, however, have suggested that the addition of testosterone may improve the response to sildenafil monotherapy, particularly in men with low or borderline testosterone levels.[25] The combination of testosterone and sildenafil was also effective in treating ED in eight bone marrow transplantation recipients with severe primary hypogonadism.[26] A role for testosterone supplementation in diabetic men who do not achieve a satisfactory response to sildenafil has also been suggested,[27] as hypogonadism is prevalent in diabetic men, particularly older patients.[28,29] Although studies of combination therapy with testosterone and alprostadil have not yet been reported, this combination may also have the ability to improve ED.

In a study in which intracavernous alprostadil was compared with intraurethral alprostadil in 111 patients with ED, intracavernous alprostadil was significantly more effective in treating ED and was preferred by both patients (69 versus 16%) and partners (63 versus 10%).[30]

Combination therapy with intraurethral alprostadil plus sildenafil has produced excellent results in preliminary studies. In a trial of 28 patients who had failed either sildenafil or intraurethral alprostadil

monotherapy, 100% achieved satisfactory erections by 30 months after initiation of combination therapy.[31] A study of 65 private practice people with ED who had failed both sildenafil and alprostadil monotherapy produced similar results, with 60 (92%) reporting that they were satisfied with combination therapy.[32]

Exploiting multiple pathways involved in erections with combination therapies

As with any disorder or disease that involves multiple signaling pathways, a combination of agents that affect multiple pathways involved in ED may have potential therapeutic benefits over therapy with a single agent that promotes only 1 pathway. Data suggesting that a threshold level of testosterone is essential for normal erectile function raise the possibility that combination therapy with testosterone and other ED agents, either oral, local, or both, could produce excellent results in certain subsets of patients. As the median age of the population continues to increase, hypogonadism, type II diabetes, and ED will also become more prevalent. The future role of testosterone in treating ED may thus be substantial. Other combination therapies that exploit multiple pathways, such as PDE5 inhibitors plus alprostadil, may also provide valuable treatment options for patients refractory to monotherapy for ED.

Discussion

Dr Lisa Tenover: How often would testosterone work alone, without sildenafil, in older men?
Dr Ridwan Shabsigh: Not frequently. Testosterone therapy alone will probably not be successful in the majority of patients with ED. However, if we think about men with low testosterone or borderline low testosterone who have failed PDE5 inhibitors, then we might be looking at significant utilization. I believe this combination of therapies may be particularly useful in men with type II diabetes, who frequently have hypogonadism.
Dr Tenover: If you had a patient with predominantly low libido without significant problems with erections, would that presentation change how you'd approach therapy?
Dr Shabsigh: In men presenting with only hypoactive sexual desire, but no ED, I think almost everyone would agree that it would be appropriate and indicated to check testosterone levels. Low sexual desire is usually caused by one of two causes: hormonal factors or psychologic factors. The branching point in the decision-making path for diagnosis is serum testosterone.
Dr Glenn R. Cunningham: Are there any potential problems with testosterone combination therapy for the treatment of ED?
Dr Shabsigh: I am not aware of any drug interactions or precautions necessary with combinations of testosterone and PDE5 inhibitors or testosterone and penile injection therapy with alprostadil. Testosterone could also be used for patients with a penile prosthesis. Just today I saw a patient who has a penile prosthesis that was implanted years ago, and now he is complaining of low sexual desire and low ejaculatory volume. However, for someone who has been treated for ED with a penile prosthesis and has low sexual desire and gets testosterone for that, these are two separate treatments for two separate conditions.
Dr Adrian Dobs: I have a question about whether there are any testosterone formulations that are particularly used for ED, or whether they all work similarly?
Dr Shabsigh: In ED, testosterone treatments in the past were mostly intramuscular injections. When the patches came out, there was a lot of enthusiasm, especially for the nonscrotal patches. The enthusiasm went away very quickly due to the high number of side effects, such as skin irritation. The recent gel formulations are attractive to urologists and people with ED because they are not injections, and the skin toleration is excellent. Gels and injectable formulations are probably the two most commonly used testosterone formulations for ED.

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