REVIEW ARTICLE

Oral therapy for erectile dysfunction: An overview

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Over the past 20 years, treat ment options for erectile dysfunction (ED) have become more effective and, despite the effectiveness of intracavernous injections, vacuum devices, surgery and other treatments, there has been a trend toward the development of less-invasive modalities. Oral drugs have become the first-line therapeutic option for many men with ED. This review highlights the pathophysiology of ED, oral therapy for ED and new drug targets for the treatment of ED products available in the market for ED.

***Key words*:** *Adrenoreceptors, erectile dysfunction, oral therapy, sublingual*

INTRODUCTION

Erectile dysfunction (ED) is of two types: Psychological impotence and organic impotence. Psychological impotence is due to mental factors. These include depression, performance anxiety, stress, relationship problems, financial difficulties and mental illness. Organic impotence is due to some form of bodily malfunction. Various causes of organic impotence include reduced blood flow to the penis; low levels of androgens, such as testosterone; and nerve damage from disorders such as multiple sclerosis, Parkinson's disease, diabetes and stroke, which affect the brain's ability to respond to sexual stimulation.

ED is the persistent inability to attain or maintain a penile erection sufficient to permit satisfactory sexual intercourse.[1] It is a highly prevalent medical condition that affects 52% of men between 40 and 70 years of age to some degree.[2] Although ED is not an inevitable consequence of aging, its prevalence and severity increase with age.[3]As the world's population continues to increase and to live longer, it is predicted that 322 million men worldwide will suffer from this disorder by the year 2025.[4]

ED treatments have evolved as a result of a better understanding of the physiology and pharmacology of erectile mechanisms. Penile erection occurs as a function of trabecular smooth muscle relaxation and a subsequent increase in blood flow to the lacunar spaces, which results in an engorgement of the penis and restriction of venous drainage. Relaxation of the smooth muscle in the corpus cavernosum relies on the coordination of several central and peripheral nervous system signaling pathways. A change from primarily sympathetic to parasympathetic activity in the penis causes nitric oxide, the principal mediator of penile erections, to be released from endothelial cells lining the blood vessels and sinusoids of the corpus cavernosum and from non-adrenergic, non-cholinergic nitric oxide-producing neurons.[5] Nitric oxide then diffuses across the smooth muscle cell membranes and activates soluble guanylate cyclase, causing accumulation of cyclic guanosine monophosphate (cGMP) and resulting in a cascade of events that leads to the relaxation of the smooth muscle and to an erection.[6]

PATHOPHYSIOLOGY OF ERECTILE DYSFUNCTION

Understanding the pathophysiology of ED has been one of the challenges of effective treatment. Two hypotheses are currently believed to most likely play a role in the pathology of ED. The first considers metabolic imbalances between contractile (norepinephrine, endothelin and prostanoids) and relaxatory factors (vasoactive intestinal polypeptide and nitric oxide) in the corpus cavernosum as the reason for ED. The greater prevalence and severity of ED that occurs with aging may be a consequence of a shifting in the structural or metabolic balance in some men.[7]

The etiology of ED involves multiple organic and psychogenic factors that often co-exist. Psychogenic factors are the most common causes of intermittent erectile failure in younger populations, but they are usually secondary to or they may co-exist with organic

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factors in older populations.[8] Other factors contributing to ED include vasculogenic, neurogenic, endocrinologic, structural (traumatic) and pharmacologic causes as well as lifestyle factors such as obesity, a sedentary lifestyle and alcohol and tobacco use. Many of the conditions that contribute to ED are chronic and systemic, involving multiple avenues of damage. These conditions include cardiovascular disease, hypertension, diabetes mellitus and depression.[9]

The unifying theme in many of the diseases linked to ED is a damaged or malfunctioning endothelium, referred to as endothelial dysfunction.[10]

ORAL THERAPY FOR ERECTILE DYSFUNCTION

The introduction of sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, heralded the beginning of oral treatment for ED.

Sildenafil

The first selective PDE5 inhibitor, sildenafil, enhances the pro-erectile effect of nitric oxide by decreasing the rate of catabolism of cGMP, thereby reinforcing the physiological signal that facilitates smooth muscle relaxation and erection.[11] Sildenafil is more selective for PDE5 inhibition than many other PDE isozymes, but it is only about 10 times more selective for PDE5 than it is for PDE6. Sildenafil is rapidly absorbed, reaching maximum plasma concentrations within 30-120 min of oral dosing in the fasting state. The elimination half-life of sildenafil and its major active metabolite is approximately 4 h, and no more than one dose should be taken in a 24-h period.[12]

Sildenafil has been reported to significantly improve the symptoms of ED with varying etiologies and levels of severity.[13] However, no data on the subsequent rate of satisfactory intercourse have been provided. Sildenafil is reported effective and well tolerated in patients with diabetes[14,15] and in those with cardiovascular disease, including those taking beta-blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers or a combination of these.[16] Evidence also exists that sildenafil is effective in men with Parkinsonism[17] and Spina bifida.[18]

Sildenafil is generally well tolerated, with most adverse events being transient, and mild to moderate in severity. The majority of sildenafil-associated adverse events are vasodilatory in nature (e.g., headache, flushing, nasal congestion), with gastrointestinal (dyspepsia) and visual (abnormal color vision) adverse events reported less frequently,[19] although they have been greater in fixed-dose studies. Sildenafil can potentiate the vasodilatory properties of nitrates; therefore, its administration is contraindicated in patients who use nitric oxide donors or nitrates in any form.[11]

Dopamine agonists

Sublingual apomorphine enhances central pro-erectile mechanisms by binding to dopamine receptors in the paraventricular nucleus of the hypothalamus. In clinical trials, apomorphine was found to be effective in patients with ED of various etiologies and levels of severity, although with substantially less efficacy than any of the PDE5 inhibitors.[20] The adverse events reported were nausea, headache and dizziness. The sublingual formulation of this drug permits rapid absorption and a rapid onset of action, with an average median time of 16-23 min after dosing to attain an erection with sexual stimulation. Overall, sublingual apomorphine meets the criteria to be a first-line treatment for ED.[21]

Yohimbine and phentolamine

The stimulation of adrenoreceptors is considered the main mechanism of cavernosal smooth muscle contraction and antagonizing anti-erectile mechanism with alpha-adrenergic receptor antagonists is a potential treatment for ED.[21] Yohimbine, a naturally occurring alkaloid agent derived from the bark of an African tree, has been used as an aphrodisiac and erectogenic drug for many years. However, the use of yohimbine for the treatment of ED remains controversial, because the drug has not been assessed in rigorous clinical trials.[22] Phentolamine is an 1- and 2-adrenergic receptor antagonist. Clinical trials have demonstrated that oral phentolamine may have a beneficial effect on erectile function. It should be noted that this ban has been lifted by the United Kingdom and that patients there may be recruited again into clinical trials.

Tadalafil

Tadalafil is a potent and selective PDE5 inhibitor being reviewed for the treatment of ED. Tadalafil is rapidly absorbed, with a mean time to maximum drug concentration (t_{max}) of 2 h and a half-life of 17.5 h.[23] The rate and extent of absorption of tadalafil are not affected by food. Moreover, tadalafil is well tolerated. The most commonly reported adverse events were headache and dyspepsia. The unique pharmacokinetic properties of tadalafil as well as the lack of food and alcohol interaction are potentially valuable features in an ED therapy, because it may improve ease of use and eliminate planning in a couple's sexual activity.

Vardenafil

Vardenafil is another PDE5 inhibitor that has shown superior PDE5 selectivity and potency compared with that of sildenafil. Vardenafil is rapidly absorbed, with a t_{max} of 0.7 h and a half-life similar to that of sildenafil of approximately 4 h.[24] Vardenafil's efficacy and safety have been evaluated in an at-home trial in which men with mild to severe ED took the study drug about 1 h before intended intercourse. Eighty percent of the patients taking vardenafil 20 mg reported an improvement in their erection at the end of treatment versus 30% of those who received placebo. The most common adverse events associated with vardenafil included headache,

flushing, dyspepsia and rhinitis.[25]

NEW DRUG TARGETS FOR THE TREATMENT OF ERECTILE DYSFUNCTION

RhoA/Rho kinase and endothelins

Although the precise role of Rho-kinase in the maintenance of penile erection remains to be elucidated, Rho-kinase antagonists such as Y-27632 have been shown to stimulate erection in rats and to inhibit the contraction of the corpus cavernosum in humans and rabbits.

Endothelin-1 is a potent endothelial-derived vasoconstrictor with a possible role in penile flaccidity and ED pathophysiology. Endothelin-1 and Rho-kinase antagonists may therefore prove beneficial in ED treatment.[26]

HERBS USED IN THE TREATMENT OF ERECTILE DYSFUNCTION

There are various herbs that are effective in the treatment of male infertility. These sex herbs help maintain erection longer, increase sexual desire, raise testosterone levels and increase sperm count.

Major herbs for ED treatment are:

Ashwagandha

The herb ashwagandha is sometimes called Indian Ginseng because it is thought to have similar effects on the body. It is thought to increase energy, stamina and sexual function.

Yohimbe

The bark of the yohimbe tree is a source of yohimbine, a compound that has been found to stimulate blood flow to the penis, increase libido and decrease the period between ejaculations. Yohimbe is not recommended, however, because it is potentially dangerous, even in small doses. Side effects may include dizziness, anxiety, nausea, a severe drop in blood pressure and abdominal complications.[27]

Gingko

Most of the clinical studies showed that gingko effectively helps in increasing the flow of blood to the penis. If ED is due to the intake of antidepressant medications, then you will get a great benefit by taking gingko. The study showed that 50% of the men who took gingko showed a great improvement in sustaining erections.

Ginseng

Ginseng is used for stimulation in your body without causing nervousness and stress. It has become popular for treating men suffering with ED. According to the studies, men who take ginseng for up to 8 weeks will observe a great improvement in maintaining the erections.

Saw palmetto

From many years, saw palmetto has been used as a natural cure for enlarged prostate. Also, this herb is effectively used for urinary tract infection. It is a fact that the urinary tract and prostate play a key role in ED. Thus, it is essential to maintain these areas healthy, and then only will you definitely see a progress in your ability to continue an erection.

Horny goat weed

This herbal remedy has been used in Chinese medicine for centuries. It may help raise low levels of testosterone and thyroid hormone.

Catuaba bark extract

It restores your nervous system function by bringing about increased brain function, reduced nervousness, better sleep and improved sexual function.

Cuscuta seed extract

The cuscata is commonly known as the dodder plant and it is commonly used to increase sperm production and fertility and is also used for the treatment of impotence.

Gokhru

Its primary use is for the purpose of increased sex drive by restoring hormone levels to the normal range, primarily the hormone testosterone.[28]

Damiana

It is used to relieve headaches, control bed wetting, better control of the muscles in the urinary tract, as an aphrodisiac and to enhance orgasms.[28]

CONCLUSION

Sildenafil in particular has had a profound effect on ED awareness among medical professionals and the general public and has changed the way men with ED are treated. Sublingual apomorphine, although not as effective or widely used as sildenafil, has proven to be an adequate alternative. New oral agents, such as the future generation of PDE5 inhibitors, may help obviate some of the current barriers to ED treatment. Tadalafil and vardenafil are the two newest drugs of this kind. These agents have demonstrated a high level of efficacy and good safety in clinical trials when taken by men with ED of various etiologies and levels of severity.

ED herbs are not new. In fact, a number of ED herbs and other natural remedies have been used in Chinese, African and other traditional medicine cultures for many years. But, determining whether ED herbs work and whether they are safe can be tricky.

Because the ultimate goal of therapy is to prevent or modify the disease and to provide a cure, and because no available treatment today meets these criteria, new research in this direction is needed. Although the perfect therapy for ED does

not exist, with the numerous treatments available today and in development, the future is promising. The challenge will be to identify and understand issues that are important to both the patient and his partner in order to provide them with an option that will not only safely treat the symptoms of ED but also restore their normal sexual relationship.

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