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REVIEW

ew oral therapies for the treatment of erectile dysfunction

I. EARDLEY
Pyr h Dep rtme t o rology, St J mes iversity Hospit l, Leeds, UK

Introduction

For many men who seek medical advice for erectile dysfunction the ideal therapy would be oral medication, probably involving a short course of tablets which would effectively restore sexual function to normal. Alternatively, some men might wish for a tablet which facilitated or produced an erection and which could be taken as and when required. Ideally this 'on-demand therapy' would be rapidly acting, effective, safe and in this cost-conscious age, it would also be helpful if the medication was inexpensive.

Sadly, currently such treatment is not available and most men with erectile dysfunction are treated either by injection therapy or using vacuum pumps. A significant number of men are dissatisfied with these treatments which explains, in part, why the discontinuation rates for both treatments are high. Partly for this reason there is increasing interest in the development of oral agents that might provide effective treatment of erectile dysfunction and the most prominent of these are outlined in Table 1. While the mechanism of action of these drugs is sometimes clear, on other occasions it is not. However, in broad terms, the drugs either act within the central nervous system, or they act within the penis.

Adrenoceptor antagonists

Historically, the adrenoceptor antagonist that has been in clinical use for longest is yohimbine. It is an indole alkaloid which has had a reputation as an aphrodisiac for over a century and which, in the 1960s, was widely used in combination with methyl testosterone and extract of nux vomica as a treatment for men with erectile dysfunction [1]. Only in the past 15 years have formal clinical studies have been undertaken. Following an initial pilot study in 1982, which showed a 43% response in a sample of men with mainly organic impotence [2] the same Canadian group undertook a further randomized placebo-controlled study in a similar group of men using yohimbine at a dose of 6 mg three times a day [3]. Although there was a 42.6% response rate with yohimbine, there was also a 27.6% placebo response and the differences were not statistically significant. However, a subsequent double-blind placebo-controlled partial crossover study in men with a diagnosis of psychogenic impotence did show a significant advantage for yohimbine over placebo. The positive response in the patients taking yohimbine was 62%, while in the patients taking placebo only 16% responded. However, when those who crossed over from placebo to yohimbine are included, the response rate for yohimbine fell to 46% [4]. In all these studies, around half of the responders had a complete response, while the other half had 'some improvement in the quality, frequency or rigidity of erections, but not sufficient to restore satisfactory sexual functioning'. Subsequent studies have also tended to support a possible role for yohimbine in men with psychogenic erectile dysfunction, although it is apparent that only 30–40% of men have a positive response [5,6].

Yohimbine is a reversible alpha 2 adrenoceptor antagonist. The exact site of action in men with erectile dysfunction is unknown, although it is known to have both central and peripheral adrenoceptor-blocking actions. Alpha adrenoceptors are present in the corporal smooth muscle and stimulation results in corporal contraction. Local administration of an alpha adrenoceptor antagonist, such as phentolamine, leads to corporal smooth muscle relaxation, which raises the possibility that some of the effects of yohimbine are mediated peripherally by relaxation of both the vascular and corporal smooth muscle. However, there is evidence in rats that yohimbine may also act centrally. Clonidine, a centrally acting alpha-2 adrenergic agonist, was found to inhibit sexual activity in rats when administered systemically [7]. Subsequent experiments showed a similar effect when the clonidine was administered centrally into the medial pre-optic area which is adjacent to the rat hypothalamus, and this effect was blocked when yohimbine was administered both centrally and systemically [8]. The implication is that there are alpha-2 adrenoceptors near to the rat hypothalamus which have an inhibitory effect upon sexual function.

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Table 1 The currently available drugs and their site and probable mechanism of action

Site of action	*Probable mechanism*	*Drug*
Centrally acting drugs	Adrenergic receptor blocking agents	Yohimbine
		Delquamine
		Phentolamine
	Dopamine receptor agonists	Apomorphine
		Bromocriptine
	Serotonin receptor-blocking agents	Trazadone
Peripherally acting agents	Nitric oxide precursor	L-Arginine
	Phosphodiesterase inhibitors	Sildenafil

In clinical trials, yohimbine has usually been taken continually at a dose of 15–43 mg per day in divided doses, although it has been suggested that larger doses of 20–30 mg used 'on demand' may be effective. There are no clinical trials to assess this hypothesis. Side-effects include palpitations, urinary frequency, nausea, indigestion and headaches while nightmares, panic attacks and transient hypertension have also been reported.

Recently, a similar compound, delquamine, which also acts as an alpha 2 adrenoceptor antagonist, entered clinical trial. The subjects were men with predominantly psychogenic erectile dysfunction but the trial was stopped prematurely.

Phentolamine is an alpha adrenoceptor antagonist which has been used for some time as an agent for intracorporal injections in combination with papaverine. Several years ago, a small placebo-controlled study suggested moderate efficacy for oral phentolamine in the treatment of men with non-organic impotence [9]. However, production of the oral form of the drug was discontinued for some years and only recently have these initial observations been pursued further [10]. The drug is administered orally around 15–30 min before sexual intercourse and it is currently undergoing more extensive clinical trials. However, initial results show only a marginal benefit for the medication over placebo. In a small, randomized placebo-controlled study in 44 men with organic impotence, a dose of 40 mg of phentolamine produced a response in half the patients, compared with a placebo response of 20% [11]. There were too few patients for statistical validity. In a larger study of 230 men with both psychogenic and organic erectile dysfunction, doses of up to 60 mg of phentolamine did not have any advantage over placebo [12]. A dose of 40 mg appears to be tolerated best, with minor side-effects such as tachycardia and nasal stuffiness appearing with larger doses. Again the mechanism of action may be via central effects or via a direct action on the cavernosal smooth muscle.

Dopaminergic agents

When dopaminergic agonists are administered parenterally to rats, they induce penile erection, yawning and stretching [13]. In fact, it is now clear that the site of action is the paraventricular nucleus of the hypothalamus, where the drugs act via the D2 dopaminergic receptors [14]. Apomorphine is a D2-receptor agonist which has only weak activity on D1 receptors and in the past few years there has been increasing interest in its use as an agent for the treatment of erectile dysfunction. Initially it was shown that parenteral administration resulted in erections in normal men [15] and then efficacy was reported in the treatment of impotent men [16,17]. However, side-effects such as yawning, nausea and vomiting were common, the effect was short-lived and while it could only be administered parenterally, there was little further clinical interest.

Recently, a sublingual formulation of apomorphine has been developed and clinical trials in men with erectile dysfunction have commenced. In an initial study, 49 men with psychogenic impotence were given sublingual apomorphine in the laboratory [18]. Using Rigiscan criteria, the optimum dose for most men was found to be between 4 and 6 mg. In a second part of the study, men were given apomorphine to use at home, and 70% were able to achieve successful intercourse more than half the time. Nausea occurred in 13% of those taking 6 mg of apomorphine, with vomiting in 2%. There was no change in the patient's mood or libido, although yawning was common. This formulation of apomorphine is currently entering phase-3 clinical trials in North America.

Bromocriptine is another orally active dopaminergic agent which has been used in the treatment of the sexual dysfunction associated with hyperprolactinaemia [19] and which has also been shown to be of value in men with erectile dysfunction who are on maintenance haemodialysis [20]. However, side-effects, including nausea, vomiting and hypotension, are common and often led to cessation of treatment. During these trials it was also noted that treatment was ineffective if the

pre-treatment testosterone level was below the normal range. Studies of bromocriptine in men with erectile dysfunction of other aetiologies have provided conflicting results. While early studies showed no benefit [21,22], a later study showed that oral bromocriptine was often effective in those men who had a positive response to subcutaneous apomorphine [17].

There is much more to understand about the relationship between dopamine and erectile function. For instance, it is clear that both adrenocorticotropic hormone (ACTH)-like peptides and oxytocin can induce penile erection and yawning when injected into the hypothalamus of the rat [23,24]. It appears that the responses to dopamine, oxytocin and ACTH are interrelated, and perhaps play a sequential role in the central control of erection. It may be that as we begin to understand the mechanism by which these agents produce an erection, then other oral agents may be identified as having a beneficial effect in men with erectile dysfunction.

Serotoninergic receptor antagonists

Trazodone is a widely used antidepressant, although it has also some anxiolytic, analgesic and sedative effects. After its introduction in 1982, there were several reports suggesting that it could cause priapism [25,26]. Subsequently, there were also several case reports suggesting that as an oral agent it may be valuable in the treatment of men with erectile dysfunction [27,28]. An early placebo-controlled study using a dose of 50 mg three times daily in men with erectile dysfunction of no obvious identifiable organic cause showed a definite superiority over placebo, with 65% of patients achieving a positive response rate (compared with 13.6% for placebo) [29]. The major side-effects were priapism (in a single patient) and sedation, although this was usually mild. Interestingly, trazodone was also superior to treatment with both ketanserin and mianserin, which block 5-HT_2 and 5-HT_1 receptors, respectively. The mechanisms by which trazodone produces its effects upon erection are poorly understood. It has several pharmacological actions, including as a 5-HT re-uptake blocker, but it also is known to block both 5-HT_2 receptors and α_2-adrenoceptors, and it has been suggested that this latter role is the most important one with respect to erection [30]. However, the action on 5-HT receptors may also be important, as it is known that serotonin has an important role in both facilitating and inhibiting sexual behaviour in experimental animals. For instance, activation of 5-HT_{1A} receptors facilitates sexual behaviour in rats, while 5-HT_{1B} receptor activation appears to inhibit it, and 5-HT_3 receptor activation probably inhibits sexual activity [31].

Whatever the mode of action, more recent clinical studies suggested that if trazodone does have a role in the treatment of erectile dysfunction, then its benefit may only be marginal. One randomized study showed a trend towards activity when compared with placebo, although this was not statistically significant [32], and another double-blind placebo-controlled trial showed no benefit for trazodone 150 mg over placebo [33]. There have been suggestions that it may be most effective when combined with yohimbine [34], but the evidence for this is sparse.

Phosphodiesterase inhibitors

It is now apparent that the relaxation of the cavernosal smooth muscle is largely mediated by the action of nitric oxide which originates from two sources, i.e. non-adrenergic, non-cholinergic neurons and the endothelium (where its release is stimulated by cholinergic stimulation). Nitric oxide achieves its actions by the activation of the enzyme guanylate cyclase, which is found within the smooth muscle cell and which converts guanosine triphosphate to cGMP (Fig. 1). Cyclic GMP is the active second messenger that mediates smooth muscle relaxation and its action is terminated by the enzyme phosphodiesterase (PDE), which converts it to GMP, itself inactive. There are six known isoforms of the enzyme and *in vitro* studies have shown that types 2, 3 and 5 are the predominant isoenzymes within the corpus cavernosum [35]. PDE type 5 (PGE5) is specific for cGMP and is thought to be the most important physiological regulator of cGMP levels within the corpus cavernosum [35,36]. PDE3 breaks down cyclic AMP, which also produces cavernosal smooth muscle relaxation, but its physiological role within the corpus cavernosum is

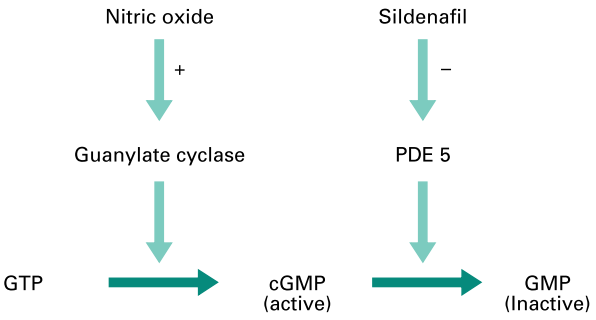

Fig. 1. Within the cavernosal smooth muscle cell, nitric oxide activates the enzyme guanylate cyclase, which converts GTP to cyclic GMP, the second messenger which relaxes the smooth muscle cell. Cyclic GMP is broken down to GMP by the enzyme phosphodiesterase type 5 (PDE-5) and sildenafil is a specific antagonist of this enzyme.

unknown. PDE2 breaks down both cyclic AMP and cyclic GMP, and again the physiological role is unclear.

Sildenafil is a selective inhibitor of PDE5 and is highly selective over the other isozymes, e.g. it has 4000 times the selectivity for PDE5 over PDE3 [35]. Early pilot studies, which were undertaken in Bristol, seemed to suggest clinical efficacy [37]. Twelve patients with erectile dysfunction of no identifiable obvious organic cause underwent Rigiscan monitoring while being exposed to visual sexual stimulation (VSS). After the administration of sildenafil, the duration of rigidity at the base of the penis during VSS was significantly greater than with placebo. In a 'home study' using regular dosing, the same men reported more erections with sildenafil than with placebo. Ten of the men reported that their erectile activity was increased with sildenafil, compared with only two when taking placebo.

Subsequent large, multicentre, placebo-controlled studies confirmed these early findings. In one study, 351 men with erectile dysfunction with no obvious organic cause were recruited to a 28-day period of using regular daily doses of placebo or sildenafil at 10, 25 or 50 mg [38]. The percentage of men who noted an improvement in their erectile response while taking placebo was 38%, while 88% of men noted an improvement in their erection on a dose of 50 mg sildenafil. A subsequent study confirmed the efficacy of sildenafil when taken in 'on demand' [39]. Forty-four men with no obvious organic cause for their impotence entered a placebo-controlled crossover study and were advised to take the medication 30 to 60 min before sexual intercourse. Again there was an advantage for sildenafil over placebo, with 92% of the men and 91% of their partners reporting an improvement in the quality of the erections on sildenafil, compared with 27% and 19%, respectively, for placebo. In a later placebo-controlled study, 233 men were given sildenafil 'on demand' for 16 weeks in a dose-escalation study and then randomized to receive either placebo or sildenafil for a further 8 weeks [40]. After 16 weeks, 58% of men were taking 100 mg of sildenafil and 29% 50 mg. Of those men randomized to receive sildenafil in the subsequent double-blind study, 75% felt that their erections had not changed or had become slightly better [41]. Of those who were randomized to receive placebo, 85% felt that there was a deterioration in their erections.

These studies were all performed in men with no obvious organic cause for their erectile dysfunction. The mean age in all the studies was 50–55 years, suggesting that while many of the men suffered from psychogenic impotence, a significant proportion might also be suffering from what could loosely be called 'age-related' erectile dysfunction, where other factors such a smooth muscle dysfunction might be relevant.

Results in men with organic impotence are more sparse at present, although again there seems to be evidence of efficacy. In one placebo-controlled study in diabetics, of those men randomized to receive placebo, 10% found an improvement in the quality of their erections, compared with 52% of men who noted an improvement with 50 mg sildenafil. More recently, a large multicentre study of 416 men with all types of erectile dysfunction (including organic causes in 73%) were randomized to receive either placebo or sildenafil at 5, 25, 50 or 100 mg. Again there was a significant advantage for sildenafil, with 29% of men reporting an improvement in their erections with placebo, compared with 78.5% of men receiving 100 mg sildenafil [42].

The drug appears to be rapidly active; a small placebo-controlled study found that the median onset of action in men who had been previously starved was 19 min [43]. It is likely that if the medication is taken after food then absorption will be delayed, with an associated delay in the onset of action. Over 95% of the compound is protein-bound and the half-life in man is 3–5 h [35]. The optimum dosage of sildenafil has yet to be determined. While the early studies used doses of up to 50 or 75 mg, in later studies much larger doses, up to 200 mg, have been used. There is evidence of increased efficacy with increasing dosage, but there is also evidence of increasing side-effects with increasing dosage and it is currently unclear exactly how high the dose can safely be. At doses of up to 100 mg, 10–20% of patients experience reversible side-effects, e.g. headache, facial flushing, indigestion, myalgia and rarely, visual disturbances, and these side-effects almost certainly reflect the presence of PDE5 in other tissues such as platelets and vascular smooth muscle. Most side-effects have been mild and transient and have not led to discontinuation of the drug.

Further large, randomized, placebo-controlled studies with sildenafil are currently underway in Europe and North America, and are primarily investigating the efficacy of sildenafil in men with erectile dysfunction of organic cause, such as diabetes, spinal cord injury and radical prostatectomy. These studies will also provide information about the optimal dosage of sildenafil and about other matters such as the development (or otherwise) of tolerance to the drug.

Other agents

A small study showed a potential role for L-arginine in the treatment of erectile dysfunction; L-arginine is an amino acid and precursor of nitric oxide, and when given in large doses it was effective in a proportion of men with erectile failure [44]. The study was uncontrolled and has not yet been followed up. Finally, there is some

suggestion that Korean Red Ginseng may also improve erectile function [45], although again this needs to be assessed in placebo-controlled studies.

Conclusion

Currently, the role of oral medications in the treatment of impotence is limited. While the clinical results with yohimbine have shown some efficacy in men with psychogenic erectile dysfunction, it has not been widely used. However, it is apparent that there are now several newer agents under clinical trial which appear to be more effective. This raises the exciting possibility that within a few years there may be an effective oral therapy for many men with erectile dysfunction. Furthermore, as the mechanisms and sites of action of these compounds differ, there is a very real possibility that combinations of drugs might be synergistic.

Is this the death knell for the injections, pumps and implants which currently form the mainstay of therapy? Certainly, it now seems possible that a significant proportion of men with erectile dysfunction will be amenable to oral therapy. However, it also seems likely that there will be many men, probably those with more severe vascular impotence, who will not respond to tablets, and it is in these men that current treatments may still be appropriate.

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