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Current Perspectives on Pharmacotherapy Treatments for Erectile Dysfunction

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1. Introduction

Erectile dysfunction (ED) is the most common sexual problem in men [1]. ED is defined as a difficulty in initiating or maintaining penile erection adequate for sexual activity. ED has a weighty effect on intimate relationships, quality of life, and overall self-esteem for men. In addition, ED may also be an early indication of undetected cardiovascular disease [2]. One of the largest current studies of ED, the Massachusetts Male Aging Study, established that the prevalence of ED increases with age as it affects up to half of the male population between 40 and 70 years old [3]. Thus, as the world's older population increases, it is estimated that the prevalence of ED will double from 152 million men in 1995 to 322 million men in 2025, indicating a dire need to reevaluate current ED therapeutic strategies [4]. In most documented cases, ED may also present with comorbidities of hypertension, diabetes mellitus, obesity, and atherosclerosis [3].

During the 1980s, most of the pioneering research in ED was sparked by the introduction of intracavernosal vasoactive drugs, which were very effective as agents inducing penile rigidity [5]. It was not until the late 1990's and early 2000's that oral phosphodiesterase-5 inhibitors were introduced, which were truly instrumental in revolutionizing the sexual medicine field [6]. Today, first-line therapy for the treatment of ED consists of orally as well as sublingually administered drugs, while intracavernosal injection (ICI), therapy, which involves direct injection of vasoactive agents into cavernosal tissue, is considered only as a second-line therapy. This chapter will discuss current perspectives on ED's pharmacotherapy and present a more in-depth review on treatments for ED, based on the works from Andersson, K.E. [7] and Uckert, S. [8].

2. First-line treatment: Oral pharmacotherapy

2.1 PDE5 inhibitors

The family of phosphodiesterases is comprised of 11 catalytic enzymes that regulate the second messenger activity in cells by cleavage of the phosphodiester bond of either cyclic adenosine monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP), or both [9]. PDE5 is present in high concentrations in the smooth muscle of corpora cavernosa of the penis and in the smooth muscle of the pudendal arteries; therefore, phosphodiesterase 5

inhibitors (PDE5) are the major initial line of pharmacotherapy for erectile dysfunction (ED). PDEs are orally active agents that are taken, on demand, prior to sexual intercourse [9]. PDE5 was discovered by Corbin and colleagues [3, 4]. The PDE5 enzyme is a homo-dimer with two identical subunits, and each subunit is 100,000 kilo Daltons. Both subunits have a catalytic domain and a regulatory domain; however, it is the catalytic domain that is the main target for PDE5 inhibitors [9]. Nevertheless, it was the discovery of nitric oxide (NO) and cGMP as the major effectors in penile smooth muscle relaxation that led to the identification of PDE5 inhibitors that can further elevate intracellular levels of cGMP [10-11]. Most PDE5 inhibitors have a comparable structure to sildenafil; in addition, a part of the molecular structure of most PDE5 inhibitors bears resemblance to the cGMP structure. This is of significance since PDE5 inhibitors are competitive antagonists of both cGMP and PDE5 [7].

The actions of PDE5 inhibitors are often described in terms of their selectivity when compared to other PDE inhibitors. The selectivity of PDE5 inhibitors is a key factor since studies have shown that some PDE5 inhibitors may cross-react with PDE6, (predominant phosphodiesterase in the retina), causing visual disturbances; for example perception of bluish haze and increased light sensitivity, has occurred in some patients [12-13]. Additionally, some PDE5 inhibitors also cross-react with PDE11; PDE11 is mainly located in cardiac, testicular and pituitary tissues of the heart and testes; however, the consequences of this cross-reaction are unknown [7]. The normal pathway for penile erection is by sexual stimulation, which releases NO at nerve endings in the penis whereby increasing the blood supply to the penis. NO, the major vasodilatory agent causes this increase in blood by diffusing into vascular smooth muscle cells in both the penile corpus cavernosum and the pudendal arteries to cause stimulation of guanylyl cyclase (GS). Elevation of cGMP in these cells leads to the activation of cGMP-dependent protein kinase (PKG), a lowering of intracellular calcium, resulting in smooth muscle relaxation. PDE5 inhibitors act by selectively enhancing erectile function by penetrating into smooth muscle cells and inhibiting PDE5, resulting in decreased breakdown of cGMP, thus PDE5 inhibitors increase blood flow of the smooth muscle by increasing relaxation, allowing for an erection to occur [9, 14]. PDE5 inhibitors are degraded in the liver, since they are not metabolized by any other enzymes in the smooth muscle cells of the corpus cavernosum. So, PDE5 inhibitors must be transported to the liver in order to be degraded. This is important to note, as it determines the duration of action, because the disappearance of the inhibitor from the plasma may indicate, but does not always prove, its clearance from the cells in which its effects were produced [9].

PDE5 inhibitors are the most widely used treatment for ED and their efficacy have been rigorously evaluated in numerous clinical trials [8]. Subjects receiving a PDE5 inhibitor report erections adequate for sexual intercourse [8, 15]. However, PDE5 inhibitors seem to be less effective in studies where male subjects have comorbid diseases such as diabetes [16]. Nevertheless, PDE5 inhibitors remain the primary line of oral treatment, and the most common reported side effects include headaches, dyspepsia, and nasal congestion [17-19]. In regard to cardiovascular (CV) safety, PDE5 inhibitors have proven to be safe in patients with CV disease; however, due to their mechanisms of action, PDE5 inhibitors are contraindicated in ED patients taking nitrates due to unpredictable hypotension [8]. On the other hand, it should be noted that the interaction between organic nitrates and PDE5 inhibitors varies according to the PDE5 inhibitor and the nitrate used [7].

2.1.1 Sildenafil

Since the launch of sildenafil as an effective basis for the treatment of ED in 1998, similar agents have undergone clinical trials and have been subsequently introduced into clinical practice [14]. There is clear evidence that sildenafil is efficacious in the treatment of ED for the broad population of men [20]. As a result, sildenafil has proven effective in cases when ED has arisen as a consequence of comorbid diseases such as diabetes, depression, cardiovascular disease, hypertension and lower urinary tract infections [9].

Sildenafil has shown efficacy when taken at doses of 25, 50, or 100 mg and has an onset of action usually within 25–60 minutes; however, absorption of the drug is slowed with food [9, 14, 21]. Minor side effects do occur with the use of sildenafil; the most reported side effects were headaches, flushing, indigestion, and visual changes [9, 19, 22]. Sildenafil will most likely continue to be the drug of choice for physicians, since there have not been any reports that have cast uncertainty on its safety for men with ED.

2.1.2 Udenafil (DA-8159)

Udenafil (DA-8159) is a PDE5 inhibitor; it is a long-acting drug with a half-time ($t_{1/2}$) of 11–13 hours, and it has a relatively fast absorption with the plasma concentration after ingestion reaching its t_{max} , that is, its peak drug level, in 1–1.5 hours [4]. Phase II clinical trial data revealed that in men with mild-to-severe ED, udenafil produced a considerable improvement in erectile function after 12 weeks of treatment [8]. A phase III study in Korea evaluated the efficacy and safety of udenafil in ED patients. All responses to udenafil were significantly greater than the placebo ($p < 0.0001$) and patients receiving either udenafil doses of 100 mg or 200 mg were significantly ($p < 0.0001$) more satisfied with their sex life compared with men taking the placebo [4]. In animal studies, the administration of DA-8159 (0.3 or 1 mg/kg) induced a dose-frequency dependent increase in intracavernosal pressure (ICP); chronic treatment with DA-8159 restored erectile responses induced by electric stimulation, improved endothelial function, and significantly decreased plasma levels of both endothelin, (a potent vasoconstrictor), and asymmetrical dimethyl arginine (ADMA), (an inhibitor of NO production) [8]. Udenafil has been reported to be a well tolerated, since most of the adverse side effects were flushing, upset stomach and headaches, which were generally mild to moderate [4, 8].

2.1.3 Avanafil

Avanafil is a pyrimidine derivative synthesized to be a highly selective PDE5 inhibitor for the treatment of ED [9]. Studies have shown that up to 84% of avanafil doses resulted in sufficient erections for sexual activity, as compared to placebo [8]. In clinical trials, avanafil showed a higher selectivity, almost 120-fold, against PDE6 than both sildenafil and vardenafil [4]. Additionally, when compared with sildenafil, vardenafil, and tadalafil (described later), avanafil's chemical structure is distinctive from the standard nucleic base/sugar/phosphate diester model; avanafil's molecular structure is a nitrogen derivative of a pyrimidine carboxamide where the nitrogen atom of the amide substituent is bound to a pyrimidinylmethyl group [8]. As a result of its unique chemical structure, theoretically, avanafil can bind to the catalytic site of PDE5 regardless of the spatial orientation of the

molecule, significantly increasing the effectiveness and affinity of the inhibitor for PDE5 [8]. In the pharmacokinetic evaluation of this drug, studies reported rapid absorption with a t_{max} approximately 35 minutes and a short $t_{1/2}$ of less than 1.5 hours without any unwanted accumulation of the drug [4]. Favorable data from a nitrate interaction study showed only a modest impact on blood pressure and heart rate [23-24].

2.1.4 Lodenafil

Lodenafil carbonate is a newer PDE5 inhibitor; it is a dimer formed by two lodenafil molecules linked by a carbonate bridge [11]. After ingestion, the carbonate bridge is broken delivering the active lodenafil compound [8, 25]. The effects of lodenafil have been extensively investigated in vitro; the drug was noted to cause concentration-dependent relaxation of both rabbit and human corpus cavernosum tissue by amplifying the NO-dependent relaxation of the penile tissue in response to acetylcholine or transmural electrical field stimulation (EFS) [8]. In comparison lodenafil was shown to be approximately twofold more potent than sildenafil for inhibition of the breakdown of cGMP [26]. Its efficacy and safety at doses of 20 mg, 40 mg and 80 mg was also tested and shown to significantly improve erectile International Index of Erectile Function domain scores (IIEF domain scores: a widely used, multi-dimensional self-reporting instrument for the evaluation of male sexual function), with only mild to moderate adverse reactions such as headache, flushing, visual disorders, and dyspepsia [9, 26]. Lodenafil is an attractive pharmacotherapy agent for the treatment of ED [25-26].

2.1.5 Tadalafil

Tadalafil has proven to be efficacious in a number of special populations of men in which ED is due to a variety of conditions including diabetes, radiation therapy for prostatic cancer, spinal cord injury, and lower urinary tract infection [9, 27]. When taken at doses of 10 and 20 mg, tadalafil significantly improved erectile function and was well-tolerated, as the only reported side effects were headache, flushing, indigestion, nasal congestion, and back or girdle pain [9, 27-28]. At present there is no convincing evidence of any significant safety issues regarding cardiovascular contraindications with the use of tadalafil when taking the recommended doses of 2.5 mg and 5 mg per day [7, 28].

2.1.6 Vardenafil

Vardenafil is an effective vasoactive agent for the treatment of ED in a broad population at doses of 10 mg and 20 mg [9, 29]. Vardenafil was even able to cause adequate erections for sexual activity in special populations, where ED was a result of diabetes, chemotherapy, depression, hypertension, and spinal cord injury [9, 29]. Vardenafil has a mechanism of action similar to other PDE5 inhibitors, thus its side effects are similar to those reported by other PDE5 inhibitors such as headache, flushing, indigestion, and nasal congestion [4, 9]. Overall, vardenafil remains a highly recommended vasoactive agent, since it has been proven beneficial for a wide variety of patients with ED, and at present, there is no convincing evidence of any significant safety issues, regarding cardiovascular contraindications, with its use [7, 9, 29].

2.2 Trazodone

Trazodone is an “atypical” antidepressive agent and it selectively inhibits central 5-hydroxytryptamine (5-HT) uptake by increasing the turnover of brain dopamines [30]. Trazodone has alpha-adrenergic blocking effects (α -AR) and, together with its meta-chlorophenylpiperazine (*m*-CCP) metabolite, trazodone is known to induce erections in animal studies by selectively blocking the α -AR receptors and by increasing the spontaneous firing rate of cavernosal tissue nerves [31]. Despite its promising mode of actions within the cavernosum tissue, trazodone is not an effective treatment for most men with ED, since orally administered trazodone has been associated with high frequencies of priapism [32]. Furthermore, in a double-blind, placebo trial trazodone was not effective even at high doses of 150 to 200 mg per day [30, 33-34]. However, trazodone is still a viable option for men with psychogenic ED, resulting from anxiety or depression [33-34].

2.3 Melanocortin receptor agonists (PT-141)

PT-141 was initially produced as a tanning agent; however it was discovered, when it was injected subcutaneously, to initiate potent erections in men with nonorganic ED [35-36]. PT-141 is a synthetic cyclic nonselective melanocortin receptor agonist, with a high affinity to MC receptors 1, 3, and 4, and it is believed to be a metabolite of melanotan-II (MT-II) [36]. Theoretically, MC receptor agonists may have beneficial effects in patients with ED based on the results from a double-blind, placebo-controlled study in which PT-141, at doses ranging from 4 to 20 mg, was administered to 32 healthy subjects [37]. Results from this study showed that PT-141 significantly increased erectile activity even without visual sexual stimulation, compared with placebo-treated subjects. Additionally, in a placebo-controlled crossover trial, men with mild to moderate ED, treated with PT-141 together with visual sexual stimulation, experienced a threefold increase in erectile activity when compared to the placebo [37]. Co-administration of PT-141 with sildenafil 25 mg significantly increased penile rigidity when compared with sildenafil alone [7, 37]. It was also noted that, when patients took the two drugs in combination, there were no significant increase in the side effects, compared to those experienced, when taking either sildenafil or PT-141 alone [7].

2.4 Potassium-channel Openers

Potassium channel openers such as pinacidil, cromakalim, lemakalim, and nicorandil have all been shown as efficacious in achieving erections in men with ED [7]. Potassium channel openers work by hyperpolarizing the cell membrane, which increases the cell membrane permeability to potassium ions causing relaxation and subsequent erection [7]. Presently, clinical experience with these potassium channel openers for treatment of ED is limited; therefore, potassium channel agonist drugs have not been approved in controlled clinical trials as an alternative treatment for men with ED [7].

2.5 Rho-kinase inhibitors

Smooth muscle contraction and relaxation is related to the level of free cytosolic calcium, which is partly regulated by the accumulation of intracellular secondary messengers such as inositol triphosphate (IP₃) and diacylglycerol (DAG) via phospholipase C (PLC) activation [3]. PLC activation facilitates the release of and the increase of intracellular Ca²⁺

concentration, resulting in calcium binding to calmodulin and subsequent activation of myosin light chain kinase [3]. When intracellular calcium levels decrease, RhoA, a small monomeric G protein, activates Rho-kinase; in turn, Rho-kinase phosphorylates and simultaneously inhibits the regulatory subunit of myosin light chain phosphatase [3, 38-39]. Thus, Rho-kinase is considered essential to the cell calcium sensitization system as its activation creates a cascade whereby the phosphorylation of myosin light chains triggers cycling of myosin cross-bridges along actin filaments, generating a contractile force that is maintained, unless inhibited, within the corpus cavernosum tissue [38]. It was first shown by Chitaley, K., et al. that Rho-kinase contributes to smooth muscle tone in the corpus cavernosum [40]. Injection of the Rho-kinase inhibitor Y-27632 into cavernosal sinuses increased intracavernosal pressure within minutes in a dose-dependent manner, without significantly decreasing systemic blood pressure [40]. Furthermore, the increase in intracavernosal pressure with Rho-inhibition was independent of the relaxing effects of N.O. and of guanylate cyclase, indicating that the Rho-kinase pathway may be an alternative therapeutic target for treating ED [38, 40]. In animal studies the Rho-kinase inhibitor fasudil, was effective against vasculogenic ED, in addition it was capable of reducing levels of pelvic atherosclerosis [41]. In a recent study involving diabetic-associated ED in rats, it was shown that chronic administration of fasudil was more effective, than other popular ED treatments, at reversing the damaging biochemical changes invoked by high insulin levels [42].

Human clinical trials have recently reported that low-dose atorvastatin (*Lipitor*), (a drug which works by inhibiting HMG-CoA reductase, an enzyme found in liver tissue, that plays a key role in production of cholesterol in the body), normalizes the diabetic response to sildenafil in streptozotocin (STZ) treated diabetic rats [43]. This result suggests that statins may also have inhibitory actions in the RhoA/Rho-kinase mechanism [42-43].

2.6 Alternative treatments for ED

2.6.1 HERBAL treatment for ED (Yohimbine)

Though herbal medicines are not a prescribed option of choice for patients in the United States, in other parts of the world like Asia, Africa and the Middle East, it is a widely used form of therapy for men with ED [44]. However, although there are a myriad of herbal treatments that are very appealing for patients with ED, caution must be warranted, since some herbal medicines may cause deleterious drug interactions, especially in men with comorbid diseases such as CV and diabetes. On the other hand, the herbal or traditional therapeutic approach may be more culturally acceptable with some patients, who may prefer this holistic option because of religious, social, monetary or other personal preferences. As a result, there is a growing interest among the population for alternative holistic treatment options, which has increased demand for such therapies in the United States [44]. Though there are many herbal remedies available at present for ED, this review will focus on the efficacy of yohimbine.

Yohimbine is an alkaloid derived from the African yohimbe tree (*Pausinystalia yohimbe*) [44]. Yohimbine has been well characterized as an alpha-2 adrenergic receptor (α_2 -AR) antagonist [44]. It specifically inhibits the pre-synaptic α_2 adrenergic receptors in the brain; as a result there is a reduction of sympathetic tone since the brain and spinal cord noradrenaline levels are diminished [45]. The plasma half-life of yohimbine was found to be 0.6 hours, whereas

the plasma noradrenergic effects of the drug lasted for more than 12 hours [46]. Theoretically, yohimbine should be a very effective treatment for ED; nevertheless, in several controlled trials on patients with different types of ED, yohimbine only produced modest effects [7]. However, a comprehensive systematic review demonstrated the advantage of yohimbine over a placebo in the treatment of ED [44, 47]. In combination with other drugs, oral yohimbine (15 mg daily) with trazodone (50 mg daily) was found to be a safe and effective treatment for psychogenic ED [44]. Despite its growing popularity, yohimbine is not currently recommended in most guidelines for management of ED, due to conflicting clinical reports concerning its efficacy [7].

2.6.2 Antioxidant therapy (Quercetin)

Oxidative stress occurs when there is an imbalance between pro-oxidants and antioxidants' ability to scavenge reactive oxygen species (ROS) [48]. ROS rapidly inactivate NO, thereby limiting its ability to relax smooth muscle [49]. Studies have also demonstrated that ROS have a central role in inducing apoptosis in cavernosum tissues [49-50]. Thus, there is overwhelming evidence implicating the role of oxidative stress in the pathophysiology of ED [48]. As a result, antioxidant treatment to regulate ROS is being explored as a potential therapeutic treatment for ED [49].

Quercetin (pentahydroxyflavone) is the most abundant flavonoid in the human diet, and it is available without a prescription as a dietary supplement [51]. Flavonoids are plant phenolic compounds with strong antioxidant properties, and they are found in various dietary sources, such as tea, onion, and broccoli. Quercetin is a potent anti-oxidant, and its mechanism of action involves the direct scavenging of free radicals such as hydrogen peroxide and superoxide, the inhibition of the pro-oxidant enzyme xanthine oxidase, the inhibition of lipid peroxidation, the chelating of iron and the altering of the anti-oxidant defense pathways in the cell [51-52]. Given its beneficial effects against oxidative damage, quercetin was hypothesized to be effective in the treatment of ED, in particular ED as a result of diabetes mellitus [51-52]. Animal studies have revealed that quercetin treatment effectively improved intracavernosal pressure of diabetic rats by preserving superoxide dismutase (SOD) activity, (an antioxidant enzyme), while simultaneously increasing endothelial nitric oxide synthase (eNOS) expression. The results clearly demonstrate that eNOS expression and NO levels in corpus cavernosum were significantly increased in diabetic rats, in response to quercetin treatment [52]. Though these studies show a promising potential for quercetin, more investigations are needed to establish its efficacy in human penile tissue.

3. Second-line treatment: Intracavernosal pharmacotherapy

Intracavernosal injection (ICI) is a second-line therapy that is mainly considered for patients who fail to respond to first-line therapy or those who cannot use the least invasive forms of currently available pharmacotherapy [53]. The ideal candidates for ICI therapy are those who use nitrates or could potentially use nitrates, have neural injury from pelvic surgery, trauma, diabetic patients, and patients who desire rapid onset of erection, greater rigidity and or duration of erection [54]. Contraindications for ICI therapy include patients with a history of priapism with vasoactive drug use, and those with severe penile fibrosis with the use of monoamine oxidase inhibitors (MAOIs); in addition, a nonresponse to ICI occurs mostly as a result of an inadequate dose, misdirected injection into the subcutaneous or

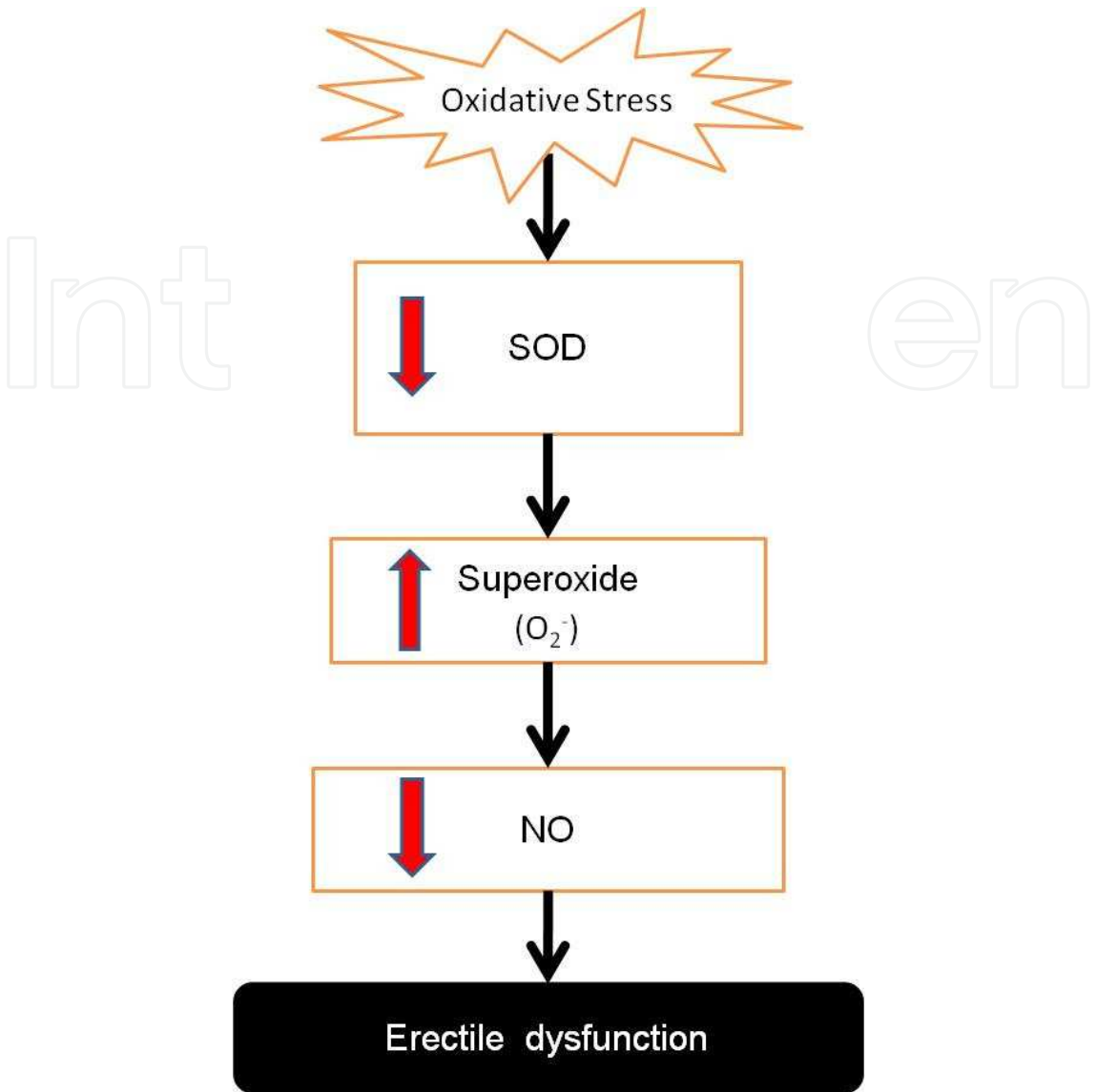


Fig. 1. SOD in the Pathophysiology of Erectile Dysfunction: During oxidative stress, SOD expression decreases causing an increase in superoxide (O_2^-). As O_2^- rises within the cell, NO production is attenuated leading to ED.

trabecular regions of the penis, leakage of vasoactive agent prior to ICI and insufficient sexual stimulation, or premature ejaculation [54].

Following an ICI and sexual stimulation, penile rigidity is achieved usually within 5–10 minutes, as a rapid increase in cavernosal artery blood flow leads to compression of subtunical venules located between the smooth muscle of the *corpora cavernosa* and the inner *tunica albuginea* (3). With venous outflow blocked, intracavernosal pressures can be greater than 100 mmHg. Vasoconstriction and the loss of penile rigidity occur as a result of an increase in sympathetic tone coincident with ejaculation (3). For ICI therapy, the most commonly prescribed vasoactive agents are prostaglandin E-1 (PGE-1), phentolamine, and papaverine (1, 3). However, with advances in medical research, other effective treatments are currently available, such as vasoactive intestinal polypeptide, calcitonin gene-related peptide, and guanylate cyclase activators.

3.1 Papaverine

Papaverine was discovered by Merck in 1848, it is an opium alkaloid originating from the poppy *Papaver somniferum*. In the treatment of ED, intracavernosal papaverine injection was the first pharmacological agent proven to be a clinically effective therapy for ED (1). Papaverine induces relaxation of the corpus cavernosal smooth muscle tissue and pudendal artery leading to penile erection via nonspecific inhibition of phosphodiesterase, leading to increased intracellular levels of cGMP and cyclic adenosine monophosphate (cAMP) (1). In *in vitro* studies, papaverine was shown to increase relaxation not only in isolated corpus cavernosum smooth muscle strips, but also in penile arteries and penile veins; in addition, these studies have also shown that papaverine was able to attenuate contractions induced by stimulation of adrenergic nerves and exogenous noradrenaline [9]. Papaverine may also regulate corpus cavernosum smooth muscle tone via a cAMP independent pathway by the inhibition of voltage-dependent L-type calcium channels [9, 55].

Although papaverine is an effective and inexpensive treatment for ED, compiled reports have implicated the use of papaverine with an increased rate of priapism and fibrosis [20, 56-57]. Penile pain is also very common following administration of papaverine [57-58]. Papaverine may cause other side effects such as flushing, sweating, upset stomach, loss of appetite, diarrhea, constipation, and irregular heartbeat [9, 59]

3.2 Alpha-adrenoreceptor antagonist (*Phentolamine*)

Although the beneficial vasoactive effects of phentolamine were discovered in the 1970s, the current clinical use of this drug is limited to use as a component of other vasoactive drug combinations [20, 60]. In the penile corpus cavernosum, there are at least three important alpha-adrenoreceptor iso-forms: $\alpha 1A$, $\alpha 1B$, and $\alpha 1D$. All three subtypes have been detected and the $\alpha 1A$ and $\alpha 1D$ proteins have been identified as the predominant subtypes in the *corpus cavernosa* [61-62]. However, the distinction and role of each individual receptor subtype to cell signaling pathways in erectile function remains mostly undetermined [63].

Alpha-1 and $\alpha 2$ -adrenoreceptors are classified as G-protein coupled receptors which initiate several complex downstream processes [61]. It has been suggested that alpha 1 receptors preserve the penile contractile tone by increasing intracellular calcium levels followed by extracellular calcium influx [61]. It should also be noted that the α -adrenergic receptor system plays a critical role in the modulation of penile flaccidity (8). Contraction induced by post-junctional $\alpha 2$ -receptors is caused by increased intracellular calcium but also involves the recruitment of ion channels, activation of phosphodiesterases and attenuation of adenylate cyclase activity [60, 64].

Phentolamine mesylate produces an α -adrenergic blockade; it is a nonselective α -adrenoreceptor antagonist with a similar affinity for $\alpha 1$ and $\alpha 2$ -adrenoreceptors; it also has direct, positive inotropic and chronotropic effects on cardiac muscle, as well as vasodilator effects on vascular smooth muscle [20]. Although ICI of phentolamine increases corporal blood flow, a concurrent increase in noradrenaline prevents sinusoidal relaxation [65]. Studies have also shown that phentolamine induces the relaxation of corpus cavernosum erectile tissue independently of $\alpha 1$ and $\alpha 2$ -adrenoreceptors blockades, via a noradrenergic, endothelium-mediated mechanism suggesting NO synthase activation (68, 77).

3.3 Prostaglandin E1

Prostaglandins were first characterized by Bergstrom, S., Bengt, S. and Vane, J. however, it was not until 1986 that the vasoactive effects of prostaglandin E1s (PGE-1) were described for intracavernosal use by Ishii, N. and Adaikan, PG. [20]. In 1996, PGE-1 became the first FDA-approved vasoactive intracavernosal drug for the treatment of ED, and its efficacy has been confirmed in three multi-centered, randomized prospective clinical trials with a six-month open-label extension [66]. Since then, a vast body of knowledge has described the efficacy and mechanism of this drug. Presently, PGE-1 is one of the most popular vasoactive agents for ICI therapy [67].

PGE-1 induces relaxation of human corpus cavernosum smooth muscle by regulating adenylate cyclase activity, upregulating the production of cAMP in the penis via activation of EP prostaglandin receptors, and subsequently leading to a decrease in intracellular calcium concentration, resulting in cavernosal smooth muscle relaxation [9, 20, 68-69]. PGE-1 mediated vaso-dilation occurs via gap junctions within the penis; additionally PGE-1 inhibits sympathetic activity by acting upon the presynaptic neurons, blocking the release of noradrenaline [70-72]. PGE-1 is metabolized by 15-hydroxydehydrogenase and has a blood plasma half-life of less than 1 minute, as liver, kidney, and penile enzymes all contribute to the conversion of PGE-1 to its inactive form [67]. Rates of priapism, a potentially devastating adverse effect, are low with the use of PGE-1, which makes it the most utilized injectable vasoactive agent [20].

3.4 Vasoactive Intestinal Polypeptide

Vasoactive intestinal peptide (VIP) is a naturally occurring neurotransmitter and a potent smooth muscle relaxing agent. VIP, which was isolated from the small intestine, was also first described as a specific neurotransmitter for inducing penile erection in 1986 [73]. While VIPergic nerves are most densely concentrated in the penis around the pudendal arteries, preliminary intracavernosal studies using VIP produced unsatisfactory results; however, when VIPs were used in combination with drugs such as papaverine and phentolamine, adequate penile erections were observed [9, 74]. As a result, current VIP therapy for ED is predominantly used in combination with phentolamine mesylate [20].

The effects of VIP are mediated via a specific G protein-coupled receptor (GPCR) which is linked to adenylate cyclase [9]. VIP co-localizes with nitric oxide synthase (NOS) within the perivascular and trabecular nerve fibers innervating the penis, thus regulating penile blood flow, and smooth muscle tone in the male genitalia [75]. Most of the NO and VIPergic nerves are cholinergic in nature, as they contain a vesicular acetylcholine transporter [76]. Given that the actions of VIP have been directly linked to adenylate cyclase, VIP can elevate cAMP concentrations in cavernosal tissues without affecting cGMP levels [77]. VIP has commonly observed side effects, such as facial flushing and headaches, which are frequent events characteristic of most vasoactive therapies [78].

3.5 Linsidomine chlorhydrate

Nitric oxide donors such as sodium nitroprusside (SNP) and linsidomine (SIN-1) can be used for the treatment of ED [79]. *In vivo* studies have shown that SNP and linsidomine (SIN-1) upregulates cGMP production, which increases NO release in a dose-dependent

manner [80]. NO release causes the relaxation of vascular smooth muscle as well as cavernosum smooth muscle. Even though SIN-1 has a short half-life of only 1–2 min, there is a potential to cause systemic hypotension with use of this drug [81–82]. SNP and SIN-1 have positive hemodynamic effects promoting erectile function and show long-term promise as intracavernosal vasoactive agents compared to other forms of intracavernosal treatment [83].

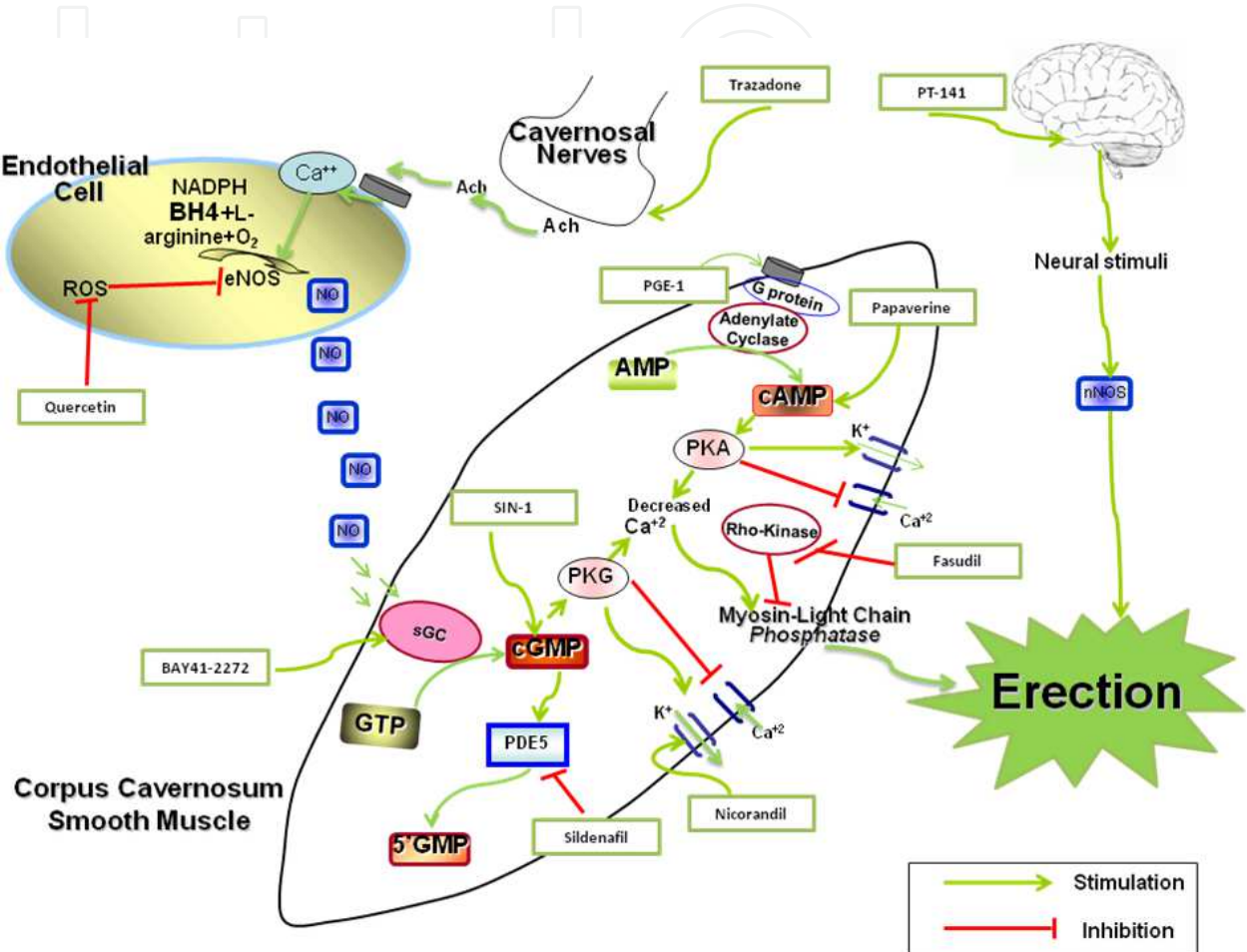


Fig. 2. **Pharmacotherapy treatments for ED:** Cavernosal nerves contribute to smooth muscle relaxation by releasing Acetylcholine (Ach). Trazadone increases cavernosal nerve firing, which increases Ach release, which stimulates eNOS, causing the release of NO. ROS causes eNOS uncoupling, which reduces its activity, however Quercetin has potent antioxidant effects and effectively reduces ROS generation. Once NO is released, it activates sGC, increasing the cGMP levels. SIN-1 and PDE5 inhibitors, such as sildenafil, also elevates cGMP levels resulting in the activation of PKG. On the other hand, PGE-1 and Papaverine elevates cAMP, causing the activation of PKA. PKG and PKA activation causes a cell signaling cascade which hyperpolarizes the cell membrane. Nicorandil also has similar hyperpolarizing effects by opening the potassium channels. Overall activation of PKG and PKA reduces intracellular calcium levels, resulting in increased activity of myosin-light chain phosphatase resulting in smooth muscle relaxation and subsequent erection. Fasudil also increases myosin-light chain phosphatase leading to smooth muscle relaxation by inhibition of Rho-kinase. Erections are also caused by neural stimulation, through the release of neuronal NO.

3.6 Calcitonin Gene-Related Peptide

Calcitonin-gene-related peptide (CGRP) causes an increase in penile arterial inflow, cavernosal smooth muscle relaxation and cavernosal outflow occlusion [84]. As a potent vasodilator, CGRP has also been shown to induce dose-related increases in penile blood flow with CGRP-specific receptor agonists [84-85]. For the treatment of ED, CGRP is usually co-administered with PGE-1, and this combined therapy has been proven successful in improving erectile function [86].

3.7 Guanylate Cyclase activator

Soluble guanylate cyclase (sGC) activators have been shown to increase intracavernosal pressure in corpus cavernosum tissue (23-24). BAY41-2272 is a sGC activator that has been shown to relax the human corpus cavernosum with or without the presence of NO (16). The sGC enzyme converts GTP to cGMP, which is activated when NO is released from erectile-autonomic nerves, resulting in smooth muscle relaxation. In the penis, cGMP is a downstream cell-signal messenger that relaxes cavernosal smooth muscle, causing adequate blood flow for penile erection (23).

4. Conclusion

ED will continue to be a problem affecting many individuals. Though there are advances in the treatment of ED, there is still a need for more effective therapy for men with complex ED caused by comorbid diseases such as diabetes. In addition, there are an increasing number of patients with cardiovascular disease for whom first-line and second-line pharmacotherapy are contra-indicated. For first-line therapy, the major drawback is severe hypotension and bothersome side effects including headaches, dizziness, vision and hearing changes, which sometimes occur during sexual activity. For second-line therapy, even though it is an effective alternative for men who cannot tolerate or respond to first-line therapy, the chief drawback of such an approach is a high attrition rate. However, although this chapter did not focus on the option of combination therapy, (the combined use of various oral vasoactive drugs and or intracavernosal therapies), this form of therapy is becoming an increasingly popular option for patients and may represent the most promising alternative for men with complex ED. At present it is very common, especially for second-line ED treatment algorithms to include combination therapy. Therefore, as we move ahead into the future, we can better understand and provide more appealing options for the management of ED, through continued combined efforts of researchers and clinicians.

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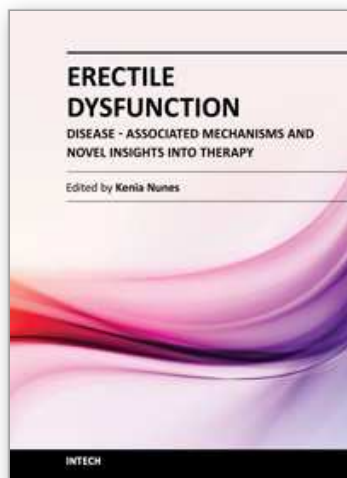
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Erectile dysfunction is a widespread problem, affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. This book contains chapters written by widely acknowledged experts, each of which provides a unique synthesis of information on emergent aspects of ED. All chapters take into account not only the new perspectives on ED but also recent extensions of basic knowledge that presage directions for further research. The approach in this book has been to not only describe recent popular aspects of ED, such as basic mechanism updates, etiologic factors and pharmacotherapy, but also disease-associated ED and some future perspectives in this field.

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