

# Pharmacotherapy for erectile dysfunction

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Erectile dysfunction (ED) is defined as the consistent inability to obtain or maintain an erection for satisfactory sexual relations. An estimated 20–30 million men suffer from some degree of sexual dysfunction. The past 20 years of research on erectile physiology have increased our understanding of the biochemical factors and intracellular mechanisms responsible for corpus cavernosal smooth muscle contraction and relaxation, and revealed that ED is predominantly a disease of vascular origin. Since the advent of sildenafil (Viagra®), there has been a resurgence of interest in ED, and an increase in patients presenting with this disease. A thorough knowledge of the physiology of erection is essential for future pharmacological innovations in the field of male ED.

Male erectile dysfunction (ED) is a condition defined by the inability to attain or maintain penile erection sufficient for satisfactory sexual intercourse. Data from the Massachusetts Male Aging Study have indicated that the prevalence of ED is 39% in 40-year-old men and 67% in those aged 70 years<sup>1,2</sup>. In the past, ED was believed to be primarily a result of non-specific psychological causes; more recently, an organic etiology can be identified in the majority of men with ED. Although patients can have several medical conditions, organic ED is usually associated with vascular risk factors, such as atherosclerosis, hypertension, diabetes mellitus, Peyronie's disease and cigarette smoking<sup>3–5</sup>. Pelvic trauma and pelvic surgery (radical prostatectomy or radical cystectomy) resulting in either vascular or nervous injury can cause ED. In addition, specific pharmacological medications, such as antihypertensive agents ( $\beta$ -blockers), diuretics, cardiac medications, hormones and antidepressants can induce ED (Ref. 4).

Basic scientific research on ED has focused mainly on the mechanisms of corpus cavernosum smooth muscle relaxation. Current pharmacotherapy for ED uses biochemical and physiological mechanisms that relax erectile tissue to achieve erectile function that is sufficient for normal sexual activity.

## Physiology of normal penile erection

The process of penile erection is dependent on an intact central and peripheral nervous system. To understand the etiologies of ED, it is essential to understand the neural and vascular pathways that function during penile erection. Normal erectile function involves three synergistic and simultaneous processes: (1) a neurologically mediated increase in penile arterial inflow; (2) relaxation of cavernosal smooth muscle; and (3) restriction of venous outflow from the penis. ED occurs as a result of the failure of any of these processes, either alone or in conjunction with each other.

The penis is composed of three bodies of tissue separated by connective tissue septae. The singular corpus spongiosum supports and protects the urethra along the ventral surface of the penis. The paired corpora cavernosa, which lie dorsally and adjacent to each other, function as blood-filling reservoirs and provide structure to the penis in the erect state. The cavernosal bodies comprise a network of vascular sinuses supplied by the helicine arteries (terminal branches

of the cavernosal arteries). In the flaccid state, the smooth muscle trabeculae, which support the vascular sinuses, are tonically contracted and permit only a small amount of arterial inflow<sup>6</sup>. The release of neurotransmitters from cavernous nerve terminals and smooth muscle endothelium in response to sexual stimulation results in cavernosal smooth muscle relaxation and ultimately penile erection.

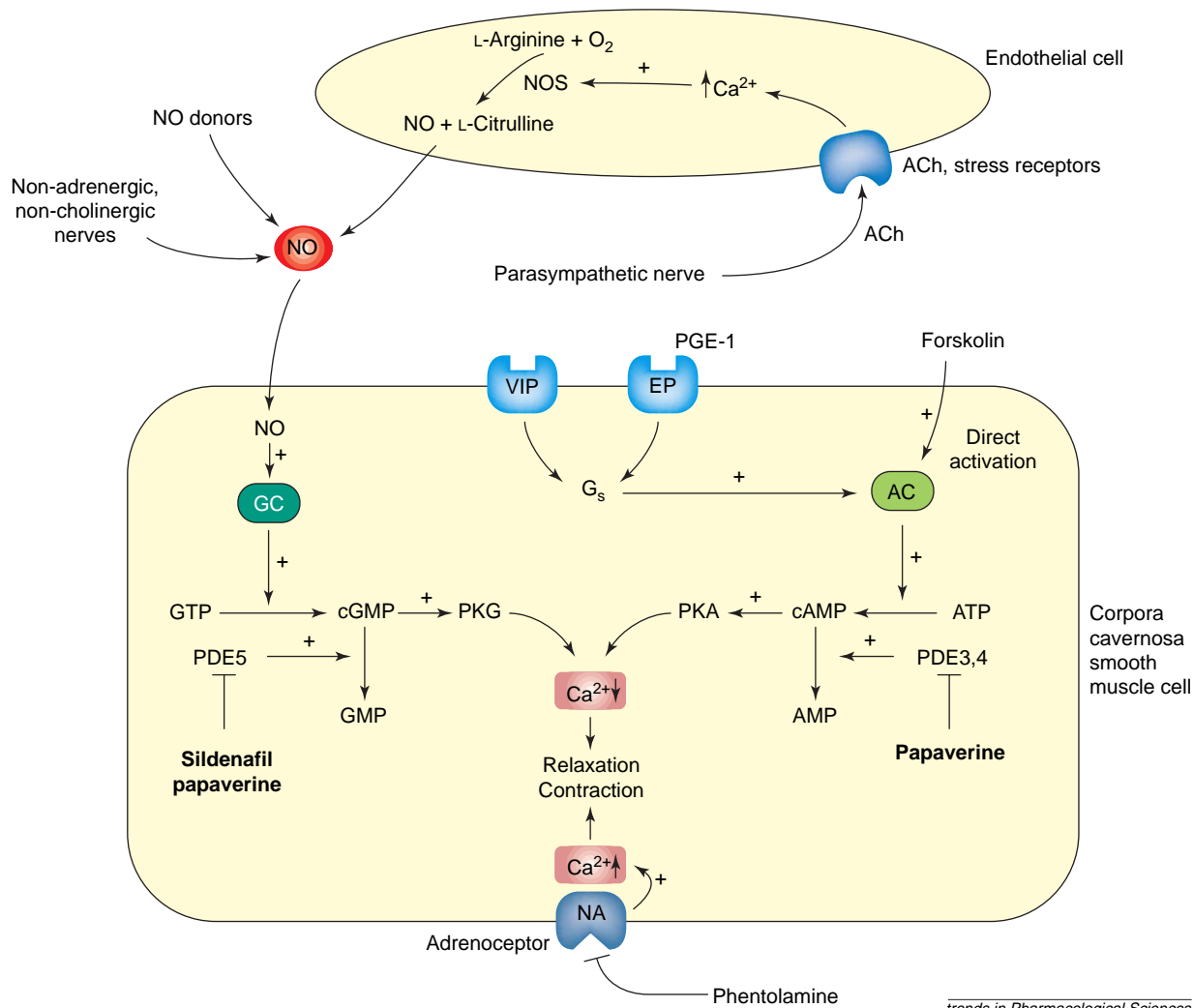
The penis is innervated by both autonomic and somatic nerve fibers<sup>7</sup>. Sympathetic and parasympathetic nerves from the pelvis merge to form the cavernous nerves, which enter the corpus cavernosum to regulate blood flow to the penis during penile erection<sup>8</sup>. The somatic pudendal nerve provides sensation to the penis. Cholinergic nerves, nonadrenergic, noncholinergic nerves (NANC), nitric oxide (NO) and other factors such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) mediate corpus cavernosum smooth muscle relaxation<sup>7</sup> (Fig. 1). In addition, shear stress and muscarinic acetylcholine receptors on trabecular endothelium stimulate the production of NO (Fig. 1). NO released from both NANC nerves and the trabecular endothelium diffuses into smooth muscle cells where it directly interacts with the soluble form of guanylate cyclase to increase intracellular concentrations of cGMP (Refs 9,10). The increase in cGMP influences several cellular processes that result in smooth muscle relaxation: (1) activation of cGMP-dependent protein kinase G (PKG); (2) activation of cGMP-dependent ion channels that reduce intracellular  $Ca^{2+}$  via  $Ca^{2+}$  sequestration and/or extrusion; (3) opening of  $K^+$  channels causing hyperpolarization of corpus cavernosum smooth muscle cells; and (4) activation of myosin light chain phosphatases<sup>11–13</sup>. Similar to the more familiar cAMP pathway, cGMP activity is terminated by hydrolysis of the 3'5' bond by the type-5 phosphodiesterase (PDE)<sup>12</sup>. Moreover, VIP, CGRP and prostaglandin-mediated pathways, which produce an increase in the concentration of intracellular cAMP, might contribute to smooth muscle relaxation in the penis<sup>7</sup> (Fig. 1). The increased corporal arterial inflow results in an increase in intracavernosal pressure and volume. As the penis expands in length and girth, the intracavernosal pressure eventually exceeds that of the subtunical venular plexus, thereby compressing it between the tunica albuginea and the peripheral sinusoids. This process of veno-occlusion results in tumescence.

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**Fig. 1.** Mechanisms and pharmacological therapies involved in regulation of corpora cavernosa smooth muscle tone and penile erection. All pharmacological agents are shown in bold. Prostaglandin E<sub>1</sub> (PGE<sub>1</sub>) and vasoactive intestinal peptide (VIP) activate adenylyl cyclase and increase intracellular levels of cAMP, resulting in cavernosal smooth muscle relaxation and penile erection. Type-3 and -4 phosphodiesterase (PDE) inhibitors prevent the breakdown of cAMP to AMP. Papaverine, a nonselective PDE inhibitor, prevents the breakdown of both cAMP and cGMP cyclic nucleotides, which leads to enhanced smooth muscle relaxation and penile erection. Forskolin activates adenylyl cyclase directly, thus increasing intracellular cAMP levels. Nitric oxide (NO), synthesized by nonadrenergic, noncholinergic (NANC) nerves and endothelial cells, diffuses into the smooth muscle cell activating guanylate cyclase and increasing intracellular cGMP synthesis, which results in cavernosal smooth muscle relaxation and penile erection. Sildenafil, the orally active type-5 PDE inhibitor, inhibits the breakdown of cGMP to GMP. Phentolamine, a nonselective β-adrenoceptor blocker, blocks the increase in intracellular Ca<sup>2+</sup> by inhibiting the activation of protein kinase C (PKC) and inositol triphosphate, thus resulting in decreased intracellular Ca<sup>2+</sup> and cavernosal smooth muscle relaxation. Abbreviations: ACh, acetylcholine; EP, prostaglandin receptor; NOS, nitric oxide synthase.

Sexual behavior and erectile function are influenced by emotional and cognitive factors. At the level of the CNS, the hypothalamic and limbic systems are responsible for the psychological components of penile erection. Within these areas, central erectogenic signals facilitate spinal cord pathways, which leads to tumescence of the penis via peripheral autonomic nerves. At the peripheral cellular level, trabecular smooth muscle tone determines if the penis is in the flaccid or erect state. The balance between contractile systems (i.e. α-adrenoceptor, endothelin, angiotensin and thromboxane A<sub>2</sub>) and vasodilatory second messenger systems (i.e. adenylyl-cyclase–cAMP and guanylate-cyclase–cGMP) determines the state of the penis and tone of corpora cavernosa smooth muscle<sup>9,14,15</sup>. One important factor that should be considered in the erectile process and that contributes to the overall vascular tone of the penis is the presence of intercellular

channels known as gap junctions in the membranes of the cavernosal smooth muscle cells<sup>16</sup>. Communication among smooth muscle cells of the corpora cavernosa allows the passage and movement of physiologically relevant ions (K<sup>+</sup>, Ca<sup>2+</sup>) and second messengers (cGMP, cAMP), which govern syncytial relaxation and contraction of the corpora cavernosal smooth musculature necessary for unified penile erection and detumescence<sup>16</sup>. Pharmacotherapy for the treatment of ED aims to develop new drug targets that inhibit the contractile systems (α-adrenoceptor antagonists) and stimulate [e.g. prostaglandin E<sub>1</sub> (PGE<sub>1</sub>), NO-donors and forskolin] or enhance (e.g. PDE inhibitors and gene therapy) the vasodilatory systems to promote increased trabecular smooth muscle relaxation of the corpora cavernosa. Here, we discuss various pharmacotherapies and their mechanisms of action for the treatment of ED.

### Vasoactive intracavernous and transurethral injection therapy

In the early 1980s, Virag and Brindley were the first to report on the clinical efficacy of intracavernosal injections of pharmacological agents to induce penile erection<sup>17,18</sup>. Since that time, intracavernosal injections of vasoactive agents have been the most reliable and effective therapy for male ED. However, intracavernosal injection can cause pain, hypotension and a local fibrotic reaction in the penis<sup>19</sup>. Direct injection of vasoactive agents into corpora cavernosa bypasses the initial psychoneurological stimuli necessary to initiate penile erection and directly causes corpora cavernosa smooth muscle relaxation by activating specific receptors and second messenger systems at the peripheral level. It is well known that cavernosal cellular responses and the tone of the smooth muscle in the penis are regulated by cAMP and cGMP (Refs 7,14,15). The cellular levels of cAMP and cGMP are determined by the relative synthetic activities of adenylyl and guanylate cyclase and the degradative activities of the cyclic nucleotide PDEs. Therefore, intracavernous vasoactive therapeutic agents use these cyclic nucleotides to mediate smooth muscle relaxation, which leads to penile erection.

#### *cAMP second messenger system and penile erection*

There have been many therapeutic agents used for the treatment of ED that elevate cAMP in the corpora cavernosa. Agents that increase intracellular levels of cAMP activate either specific cell-surface receptors that are coupled to adenylyl cyclase, or adenylyl cyclase directly (Fig. 1). PGE binds to specific PGE receptors on corpora cavernosa smooth muscle cells, which leads to elevation of intracellular cAMP via a G-protein-coupled mechanism, and activation of adenylyl cyclase<sup>14,20</sup>. Increases in cAMP result in phosphorylation and dephosphorylation of the actin-smooth-muscle-myosin cascade, which causes smooth muscle relaxation<sup>14,20,21</sup>. In addition to its direct relaxant action on smooth muscle, PGE reduces adrenoceptor-mediated vasoconstrictor tone by inhibiting the release of noradrenaline through prejunctional receptors on noradrenaline-containing neurons.

Alprostadil, a natural prostanoid synthesized from the lipid precursor dihomo- $\alpha$ -linoleic acid, is the synthetic form of PGE<sub>1</sub>. Intracavernous PGE<sub>1</sub> is the most efficacious intracavernosal drug therapy used to date for the treatment of organic ED and was the first intracavernosal agent to obtain FDA (US Food and Drug Administration) approval (Caverject, Pharmacia, Kalamazoo, MI). When PGE<sub>1</sub> is administered intracavernosally, it is metabolized largely within the corpus cavernosum and has a half-life of 5–10 min (Ref. 22). The most significant adverse factors associated with the use of intracavernous PGE<sub>1</sub> are painful erections (7–50% of patients), high cost and fear of self-injection with a needle<sup>19,22</sup>. In 1997, transurethral PGE<sub>1</sub> using a novel delivery system [medicated urethral system for erection (MUSE)] was introduced for the treatment of male ED; this method of drug delivery into the penis is less invasive and does not use a needle<sup>23</sup>. Intraurethral PGE<sub>1</sub> is absorbed

from the urethra and transported throughout the erectile tissue by communicating vessels between the corpus spongiosum of the urethra and the corpora cavernosa. The main side-effect is penile pain in approximately 11% of the patients<sup>23</sup>.

The neuropeptide VIP has long been thought to be involved in penile erection. Specific VIP receptors are present on cavernosal smooth muscle cells and mediate smooth muscle relaxation through a G-protein-coupled interaction with adenylyl cyclase<sup>24</sup>. Although VIP plays a role in tumescence, when injected alone it does not induce erections sufficient for vaginal entry<sup>25</sup>. However, when combined with phentolamine, it has moderate efficacy compared with intracavernous PGE<sub>1</sub> and has a recognized benefit of not causing penile pain<sup>26</sup>.

The 37-amino-acid peptide CGRP is a potent vasodilator that relaxes the smooth muscle cells of the corpora cavernosa by hyperpolarization via K<sup>+</sup> channel opening, and activation of adenylyl cyclase with subsequent increases in intracellular cAMP (Ref. 27). When CGRP is administered intracavernosally in patients suffering from ED, there is a dose-related increase in penile arterial inflow<sup>27</sup>. The combination of PGE<sub>1</sub> and CGRP has been used as an intracavernous combination therapy with moderate success but further studies are needed to determine the potential of this combination for the pharmacological treatment of ED.

Forskolin is a plant alkaloid that has been shown to activate adenylyl cyclase directly and increase intracellular concentrations of cAMP (Ref. 28). Unlike PGE<sub>1</sub>, forskolin does not depend on activation of G proteins but activates the catalytic subunit of adenylyl cyclase directly. This agent has been used in combination with other intracavernosal agents (e.g. PGE<sub>1</sub>, phentolamine and papaverine) for the treatment of severe vasculogenic ED but has not been used as a first-line therapy for ED (Ref. 28). Forskolin has not been approved for use in the USA because of the toxicity that occurs with repeated use of this agent.

#### *cGMP second messenger system and penile erection*

The principal mediator of corpora cavernosal smooth muscle relaxation and erectile function is NO (Refs 9,10,29). In the penis, NO is released from both nerve terminals and the endothelium that lines the cavernosal cisternae and blood vessels, and subsequently diffuses into the smooth muscle cells where it activates guanylate cyclase to increase intracellular levels of cGMP (Ref. 29; Fig. 1). This process reduces Ca<sup>2+</sup> concentration, resulting in cavernosal smooth muscle relaxation and, ultimately, in penile erection. cGMP activity is terminated by the breakdown of cGMP to GTP by the cGMP-specific type-5 PDE. In addition, NO activates the membrane-bound Na<sup>+</sup>-K<sup>+</sup> ATPase, which increases the membrane potential of the smooth muscle cells and further leads to smooth muscle relaxation<sup>30,31</sup>. The discovery of NO as the major neurotransmitter responsible for penile erection has led to the development of two classes of pharmacological agents that are used for the treatment of ED: NO-donors and -agents that increase or potentiate (PDE inhibitors) cavernosal cGMP levels.

Linsidominer (SIN-1) is the active metabolite of the anti-anginal agent molsidomine. When SIN-1 is injected into the penis, it releases NO non-enzymatically, which in turn binds to guanylate cyclase, leading to increases in intracellular cavernosal cGMP. SIN-1 hyperpolarizes the cell membrane by influencing the Na<sup>+</sup>-K<sup>+</sup> ATPase, thus making the cavernosal smooth muscle cells less responsive to  $\alpha$ -adrenoceptor-mediated contraction<sup>27</sup>. SIN-1 induces tumescence in the majority of patients and a full erection in >50% of ED patients<sup>32</sup>. No local or systemic side-effects have been reported. However, SIN-1 is less efficient at inducing penile erection satisfactory for sexual intercourse than is PGE<sub>1</sub> (Ref. 33). SIN-1 has not been approved for use in the USA; further clinical trials with SIN-1 or other NO-releasing agents are necessary to evaluate their potential as therapeutic alternatives for ED patients entering pharmacological erection programmes.

Papaverine was the first effective intracavernosal agent used for the treatment of ED. Papaverine is a nonspecific PDE inhibitor that increases both intracellular cAMP and cGMP levels, attenuates the  $\alpha_1$ -adrenoceptor-mediated contraction and, ultimately, leads to corporal smooth muscle relaxation<sup>11,24</sup>. Long-standing use of intracavernous papaverine might induce corporal fibrosis<sup>19</sup>. Moreover, when papaverine is used as a monotherapy, 15–18% patients develop priapism, most commonly men with neurogenic or psychogenic ED etiologies<sup>34</sup>. Therefore, papaverine is used in combination with phentolamine and PGE<sub>1</sub> to reduce toxicity and priapism. Future pharmacological therapies might target cAMP- and cGMP-specific PDE inhibitors in combination with other agents as alternatives to the currently used intracavernous agents because of fewer adverse side-effects.

#### *$\alpha$ -Adrenoceptor antagonists*

Phentolamine, a nonselective  $\alpha_1$ - and  $\alpha_2$ -adrenoceptor antagonist, has been used for several years as an intracavernous therapy agent. However, when used alone, this agent is weak in its ability to induce penile erection. Therefore, it is used in combination with papaverine and alprostadil<sup>21</sup>. The most common adverse side-effect is systemic hypotension and tachycardia (see below).

#### **Oral pharmacological therapies**

There has been a profound change in the current strategies for the pharmacological treatment of ED with the advent of effective oral erectogenic drugs. In the past, the first-line therapies for men suffering from ED were intracavernous and intraurethral pharmacological regimens. However, these agents have now become second-line therapies behind the oral agents. In the past, fear of injections and concern about other adverse effects from intracavernous therapy prevented several patients from seeking treatment. However, with the introduction of oral medications, public awareness of ED has increased and it has become easier to treat. Therefore, new oral agents, which involve central stimulation and peripheral facilitation of erection by using the NO-cGMP pathway, represent the future targets of non-invasive alternatives for the treatment of ED.

#### *Oral phosphodiesterase inhibitors*

The PDEs are a class of intracellular enzymes involved in the breakdown of cAMP and cGMP. At least nine families of PDE enzymes have been characterized in the human body, which suggests that each organ or tissue has its own specific pattern of PDE enzymes<sup>35</sup>. Four PDE enzymes have been characterized in human cavernosal smooth muscle: cGMP-stimulated PDE (PDE2); cAMP-specific, GMP-inhibitable PDE (PDE3); cAMP-specific PDE (PDE4); and cGMP-specific PDE (PDE5)<sup>36,37</sup>. PDE5 constitutes the majority of the cGMP hydrolytic activity in corpora cavernosa smooth muscle cells. The oral type-5 PDE inhibitor sildenafil citrate (Viagra<sup>®</sup>, Pfizer, New York, NY) is a safe and effective oral agent for the treatment of ED (Ref. 38; Fig. 1) The mechanism of action of sildenafil requires intact NO-relaxing nerve fibers and intact corpus cavernosum endothelium. Sildenafil inhibits the breakdown of cGMP induced by NO from neuronal and endothelial sources during sexual stimulation, and the increased cGMP levels enhance cavernosal smooth muscle relaxation<sup>12</sup>. Importantly, sildenafil will not be effective in the absence of sexual stimulation or in patients with vascular disease, such as diabetes or radical prostatectomy, where NO production is impaired. Moreover, sildenafil is contraindicated in cardiac patients taking nitrates because of the potential of severe hypotension<sup>12</sup>. Headache, flushing, transient visual disturbances and dyspepsia are the most common adverse side-effects with sildenafil. Interestingly, there are three new second-generation oral type-5 PDE inhibitors for the treatment of ED that are in Phase III clinical trials in the USA. These oral agents hope to offer patients less adverse side-effects. Currently, there are no cAMP PDE inhibitors available for the treatment of ED. However, both type-3 and type-4 PDE enzymes are present in the corpus cavernosum and thus, in the future, specific cAMP PDE inhibitors might be targets for the pharmacological treatment of ED (Refs 36,39).

#### *Oral $\alpha$ -adrenoceptor antagonists*

Activation of the  $\alpha$ -adrenoceptor is postulated to be involved in the suppression of erectile activity and the mediation of the contracted corpus cavernosal tone of the penis in the flaccid state. An increased  $\alpha$ -adrenoceptor-mediated tone in the trabecular smooth muscle of the corpus cavernosum has been associated with ED in older patients<sup>40</sup>. This  $\alpha$ -adrenoceptor-mediated activity is regulated by  $\alpha_1$ -adrenoceptors and prejunctional  $\alpha_2$ -adrenoceptors in the adrenergic nerve terminals and the postjunctional receptors found on corpus cavernosum smooth muscle cells<sup>40</sup>. Blockade of these  $\alpha$ -adrenoceptors might decrease the contractile function of the corpus cavernosum smooth muscle cells and facilitate erection, as well as allow endogenous vasoactive mediators, such as NO and prostaglandins, to demonstrate their vasodilatory properties in an unopposed manner.

Yohimbine, an  $\alpha_2$ -adrenoceptor antagonist with central and peripheral effects, has been used for many decades as an oral agent in the treatment of male sexual dysfunction.

However, it has limited benefits in placebo-controlled studies<sup>41</sup>. Recently, oral phentolamine, a nonselective  $\alpha$ -adrenoceptor antagonist, has been proposed to improve erections in patients with psychogenic and mild arteriogenic ED (Refs 42,43; Fig. 1). In the future, it is likely that pharmacological management of patients with ED using oral  $\alpha$ -adrenoceptor antagonists will be in combination with agents that enhance or facilitate corpus cavernosal smooth muscle relaxation.

#### Dopamine receptor agonists

Dopamine receptors, especially dopamine D2 receptors, are located in the paraventricular nucleus and medial preoptic area of the hypothalamus and are involved in sexual behavior. Apomorphine, a central D1 and D2 receptor agonist, triggers the activation of oxytocinergic and 5-HT-containing nerve endings terminating in the spinal cord. The oral route of administration of this drug is undesirable because of the high degree of hepatic metabolism. Recently, a sublingual formulation of apomorphine has been shown to be effective in improving erectile function in patients with psychogenic and moderate to severe ED (Ref. 44). At the highest doses studied, the most common side-effects of this sublingual agent are nausea and vomiting<sup>44</sup>. Interestingly, patients who experienced nausea seemed to develop a tolerance because the majority of these episodes occurred only in the first few administrations. Apomorphine is in Phase III clinical trials and is expected to be submitted to the FDA for approval in the next one to two years.

#### Future pharmacological interventions

##### Gene therapy for ED

Somatic gene therapy can be defined as the ability to introduce genetic material into an appropriate cell type *in vivo*, thus altering gene expression of that cell to produce a therapeutic effect. It has been suggested that the penis is an ideal organ for the use of gene therapy because of its external location, easy accessibility and the low turnover rate of vascular smooth muscle cells, thus allowing a desired gene to be expressed for long periods of time without affecting the systemic circulation<sup>45</sup>. Any successful gene-therapy approach to human disease requires a therapeutic gene. Garban *et al.* first demonstrated that gene therapy can be performed in the penis by using naked cDNA encoding penile inducible NOS (Ref. 46). An improvement in erectile function has been demonstrated in aged rats after injection with the gene encoding rat penile inducible NOS (Ref. 46). Christ *et al.* later showed that injection of hSLO cDNA, which encodes the human smooth muscle maxi-K<sup>+</sup> channel, into the rat corpora cavernosa can increase gap junction formation and enhance the erectile response to nerve stimulation in the aged rat<sup>47</sup>. More recently, adenoviral gene transfer of endothelial NOS was shown to reverse age-related erectile dysfunction in rats<sup>48,49</sup>. These innovative studies support the notion that *in vivo* gene transfer can have beneficial physiological effects on penile erection and might represent the future of pharmacotherapy for ED.

#### Concluding remarks

The increased public awareness of male sexual dysfunction will undoubtedly advance our understanding of the physiological mechanisms of erectile function and promote the development of new, more effective oral and local agents for the treatment of ED. The recent use of effective oral agents as first-line therapy in most ED patients has been established. Although sildenafil can cause serious adverse reactions in some individuals, such as patients with coronary disease taking nitrates, it has proved to be safe in combination with other antihypertensives. The future pharmacotherapy for male ED will focus on drugs that are non-invasive, efficacious and demonstrate limited adverse side-effects.

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## Src inhibitors: drugs for the treatment of osteoporosis, cancer or both?

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Src was one of the first proto-oncogenes to be identified and is a prototype of non-receptor type tyrosine kinases. The role of Src in bone metabolism first became apparent in Src-deficient mice and has been confirmed using low-molecular-weight Src inhibitors in animal models of osteoporosis. At the cellular level, it is well established that Src plays an important role in proliferation, and adhesion and motility. In addition, recent data indicate an involvement of Src in cell survival and intracellular trafficking in various specialized cell types. These new findings suggest that Src inhibitors might have therapeutic value in the suppression of tumor growth, tumor angiogenesis and bone resorption.

The protein tyrosine kinase Src is the prototype of a kinase family that comprises eight members in vertebrates, namely: Src, Fyn, Yes, Fgr, Hck, Lyn, Lck and Blk. In contrast to receptor tyrosine kinases, which are integral plasma membrane proteins, Src belongs to the non-receptor class of tyrosine kinases<sup>1</sup>. Src associates with various intracellular membranes, where it catalyzes the transfer of phosphate from ATP to a tyrosine residue within proteins. Src, the first tyrosine kinase to be characterized, was initially identified in the late 1970s in its viral form (v-Src) as a protein encoded by chicken Rous sarcoma virus. The cellular counterpart of v-Src, c-Src, is widely expressed in mammalian cells, with particularly high concentrations in brain, platelets and bone-resorbing osteoclasts.

The structure of Src and its regulation are well understood as a result of both mutational studies and structural models derived from X-ray crystallography data<sup>2</sup>. The N-terminus has a unique sequence but its three-dimensional structure and function are poorly defined. Two globular domains, Src homology domains 2 and 3 (SH2 and SH3), are adjacent to the N-terminus, and are involved in protein–protein interactions. The SH1 domain has tyrosine kinase functionality within a two-lobe structure (corresponding to an ATP- and substrate-binding site) that is common to other protein kinases. Within the catalytic SH1 domain, Tyr416 (in chicken c-Src) must be autophosphorylated for maximal activity, whereas the C-terminus (tail) can be phosphorylated (Tyr527 in chicken c-Src) and folded back onto the SH2 domain to produce an inactive conformation.

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