Pharmacologic Treatment of Erectile Dysfunction

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Penile erection occurs in response to cavernous smooth muscle relaxation, increased blood flow to the penis, and restriction of venous outflow. These events are regulated by a spinal reflex relying on visual, imaginative, and olfactory stimuli generated within the central nervous system (CNS) and on tactile stimuli to the penis. Drugs can have a facilitatory or inhibitory effect either on the nerves regulating this reflex or on the cavernous smooth muscle. A balance between contractile and relaxant factors governs flaccidity/rigidity within the penis. Drugs that raise cytosolic calcium either prevent or abort erection. Conversely, drugs that lower cytosolic calcium relax smooth muscle and can initiate penile erection. Efficacy in treating erectile dysfunction (ED) with phosphodiesterase inhibitors, especially type 5; α-adrenergic-receptor antagonists; and dopamine agonists exploit these mechanisms within the penis or CNS. Recent advances in our understanding of the pharmacology of penile erection are being translated into effective therapies for ED.
[Rev Urol. *2002;4(suppl 3):S17–S25*]

Key words: Penis • Erectile dysfunction • Corpus cavernosum • Smooth muscle • Cavernous nerves

Erectile dysfunction (ED) is a pervasive disorder that afflicts as many as 30 million men in the United States.[1] Yet only 6 million men seek medical attention and even fewer undergo therapy. Only 4.2 million men receive a medication for ED (Gallup Marketing Survey Information, 2001 [unpublished data]). Though 3.8 million prescriptions for the drug sildenafil were filled in the year 2000, fewer than 2.2 million men continue this drug.

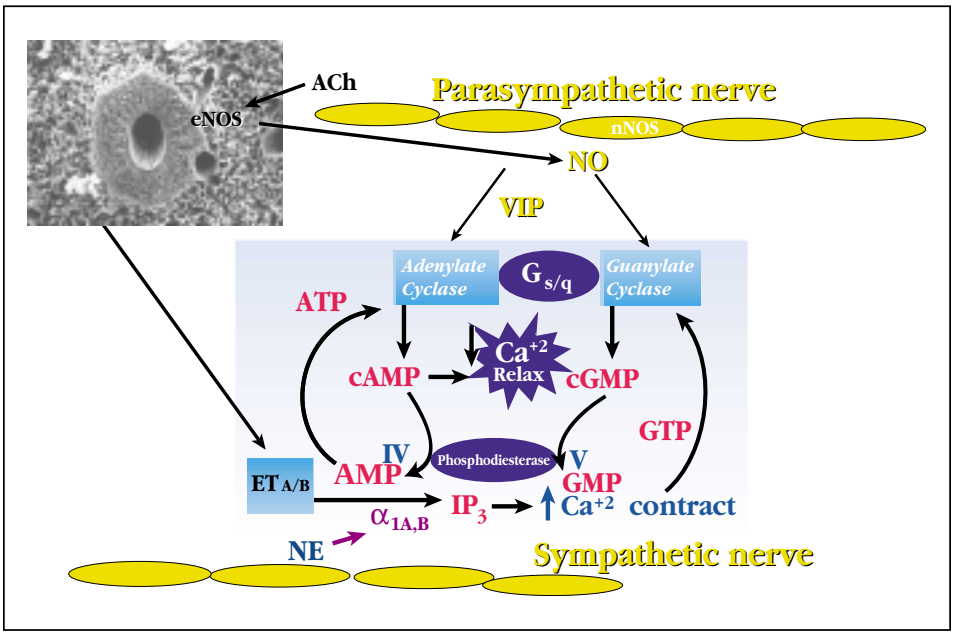


Figure 1. *Pharmacomechanical mechanisms influencing cavernous smooth muscle tone. The cavernous nerves provide parasympathetic input to penile smooth muscle. Branches of the hypogastric nerve and sympathetic chain convey sympathetic input to the penis. The cavernous nerves release nitric oxide (NO) and possibly vasoactive intestinal peptide (VIP) and acetylcholine (ACh). NO is synthesized from neuronal nitric oxide synthase (nNOS). NO acts through soluble guanylate cyclase to raise cGMP, thereby causing a fall in cytosolic Ca^{+2}, which is responsible for smooth muscle relaxation. ACh acts on vascular endothelium to release NO via endothelial nitric oxide synthase (eNOS). In addition, the endothelium produces endothelin-A (ET-A) receptors to contract cavernous smooth muscle. VIP activates adenylate cyclase, causing a rise in cAMP, with a subsequent fall in cytosolic Ca^{+2}. The breakdown of cAMP and cGMP is achieved primarily though phosphodiesterase (PDE) types 4 and 5A. Vasoconstrictive tone is provided by norepinephrine (NE) released from noradrenergic sympathetic nerves. NE acts in α_1-adrenergic receptors (α_{1A}, α_{1B}) to raise inositol triphosphate (IP_3). This elevates cytosolic Ca^{+2} and increases smooth muscle tone.*

Potential reasons for discontinuation of pharmacologic therapy include lack of efficacy, side effects, possible deterioration of underlying disease, psychogenic factors, and partner issues. Although, in general, response rates to sildenafil are high, depending on the underlying cause of ED, up to 20%–40% of patients may fail to respond to the phosphodiesterase type 5 (PDE-5) inhibition, and one recent report based on a limited telephonic survey suggests that 10%–27% of men may need to increase the dose of sildenafil to maintain effectiveness over time, and 12% of men discontinue this medication for "lack of efficacy" within 2 years. However, it remains uncertain if this is due to loss of efficacy or inadequate follow-up or control of underlying disease, because in controlled clinical studies discontinuation rates due to insufficient clinical response over 2–3 years are reported as being only 2.1%.[2] Only 1%–3% of men discontinue sildenafil because of side effects.[3] Thus, current pharmacological treatment for ED can be improved upon with regard to efficacy, pharmacokinetics, and side effects, but an equal amount of attention needs be given to the overall management of the patient to allow such therapies to deliver the optimal outcomes that they are capable of providing. This review will discuss the mechanisms whereby the categories of agents currently available or potentially useful for the treatment of ED influence penile erection.

Pharmacology of Erection

Penile erection is the result of increased blood flow to the penis, relaxation of cavernous smooth muscle, and restriction of venous outflow from the corpus cavernosum.[4] The vascular events governing penile erection rely on parasympathetic neural input derived from cholinergic preganglionic neurons residing within the sacral (S2–S4) spinal cord. Parasympathetic input to the penis occurs in response to visual, auditory, olfactory, imaginative, and tactile stimuli. The cavernous nerves arise from the pelvic nerves that exit the sacral spinal cord and supply autonomic input to the penis. These nerves release at least three neurotransmitters that are capable of relaxing the cavernous smooth muscle[4] (Figure 1). These transmitters include nitric oxide (NO), acetylcholine (ACh), and vasoactive intestinal polypeptide (VIP), of which NO is the most important.

The cavernous nerves contain neuronal nitric oxide synthase (nNOS). In nerves, nNOS synthesizes NO from L-arginine.[5] NO is released following action potential propagation along the cavernous nerve. Transgenic mice with a deletion for part of the gene for nNOS remain potent, probably as a result of the remaining isoforms for nNOS.[6] In contrast, mice deficient for cyclic guanidine monophosphate (cGMP)–dependent kinase I, or protein kinase G (PKG), fail to achieve penile erection and reproduce.[7] PKG is responsible for the signal transduction events leading to a lowering of cytosolic calcium (Ca^{+2}).

NO activates soluble guanylate cyclase within the cavernous smooth muscle cell, leading to a rise in cGMP. The rise in cGMP produces a fall in cytosolic Ca^{+2} and relaxation

of cavernous smooth muscle. In addition, NO may reduce norepinephrine (NE) release from noradrenergic nerves.[8] In the penis, the actions of cGMP are curtailed primarily by PDE-5.[9] This enzyme can exist as three isoforms in the human penis; the mRNA for PDE-5A is the most prevalent.[10] At least 12 other PDEs have been discovered.[11] PDE-5 inhibitors prolong the action of cGMP, thereby amplifying the NO signal.[5] This enhances events leading to penile erection. Competitive PDE-5 inhibitors, such as sildenafil and vardenafil, structurally resemble cGMP. PDE-5 is also found in other tissues, including the anal sphincter, gastroesophageal junction, and urethra.[11] PDE-5 inhibitors may also influence noradrenergic tone in the penis via the effects of NO on nerve terminals.

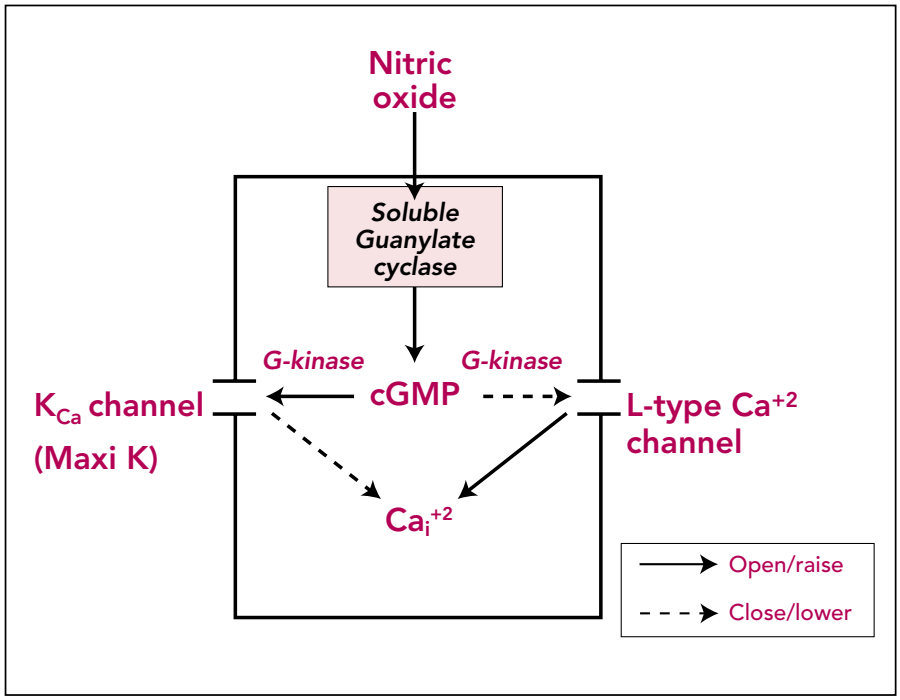
Efferent fibers within the cavernous nerves also contain ACh and VIP (Figure 1). ACh activates endothelium via muscarinic receptors of the M3 subtype.[4] Binding to M3 receptors on endothelium leads to production of NO, which is synthesized by endothelial NOS (eNOS).[12] VIP, as well as forskolin, papaverine, and prostaglandin E1, acts through adenylate cyclase to trigger a rise in cyclic adenosine monophosphate (cAMP).[5] A rise in cAMP, like a rise in cGMP, results in a fall in cytosolic Ca^{+2} in cavernous smooth muscle. This fall in cytosolic Ca^{+2} triggers relaxation of cavernous smooth muscle. In the penis, PDE-3 and 4 degrade primarily cAMP. These PDEs are also present in the myocardium. Not surprisingly, use of selective inhibitors for PDE-3 and PDE-4 in the treatment of ED is limited by cardiovascular side effects.[11]

Pharmacomechanical (receptor-mediated) mechanisms that raise either cGMP or cAMP, causing a fall in Ca^{+2}, are of potential use in treating ED. In addition, drugs acting through electromechanical mechanisms (voltage-gated channels) can relax cavernous smooth muscle and trigger penile erection. Potassium channels influence the basal tone of cavernous smooth muscle, the initiation and termination of contractile events, and relaxation because of their ability to hyperpolarize the cell (Figure 2). Hyperpolarization of corpus cavernosum prevents the influx of extracellular Ca^{+2}. Opening of two types of K+ channels in the penis, KATP and large-conductance calcium-activated potassium (maxi K), hyperpolarizes the cavernous smooth muscle cell and results in relaxation. The most physiologically relevant channel is the KCa, or maxi-K, channel. Cross talk between NO/cGMP pathways and KCa or Ca^{+2} channels may exist.

Penile erection also occurs through inhibition of contractile mechanisms.[13] Contraction of cavernous smooth muscle by NE is the result of activation of α_1-adrenergic receptors (Figure 1). Based on receptor protein levels, the penis contains α_{1A}-, α_{1B}-, and α_{2A}-adrenergic receptors in blood vessels and smooth muscle. NE released from sympathetic fibers coursing within cavernous nerves and the dorsal nerve of the penis inhibits erection.[4] Local autocrine factors such as prostaglandins and endothelins (ETs) also contract cavernous smooth muscle. The actions of ETs on cavernous smooth muscle are probably mediated by ET-B receptors.[14] The roles of ETs remain to be elucidated. These substances may influence smooth muscle contractility either directly or by modulating the effects of other substances such as NE. ETs may also influence the growth and proliferation of smooth muscle.

Increased cavernous smooth muscle tone mediated by NE and ET is the consequence of a rise in cytosolic

Figure 2. *Electromechanical mechanisms influencing cavernous smooth muscle tone. Opening of Ca^{+2}-gated potassium (K_{ca}) channels results in hyperpolarization of smooth muscle. This prevents extracellular Ca^{+2} influx. A reduction in Ca^{+2} results in relaxation of cavernous smooth muscle. Recent electrophysiology experiments suggest that NO may influence K channels as well as Ca^{+2} influx through L-type Ca^{+2} channels.*



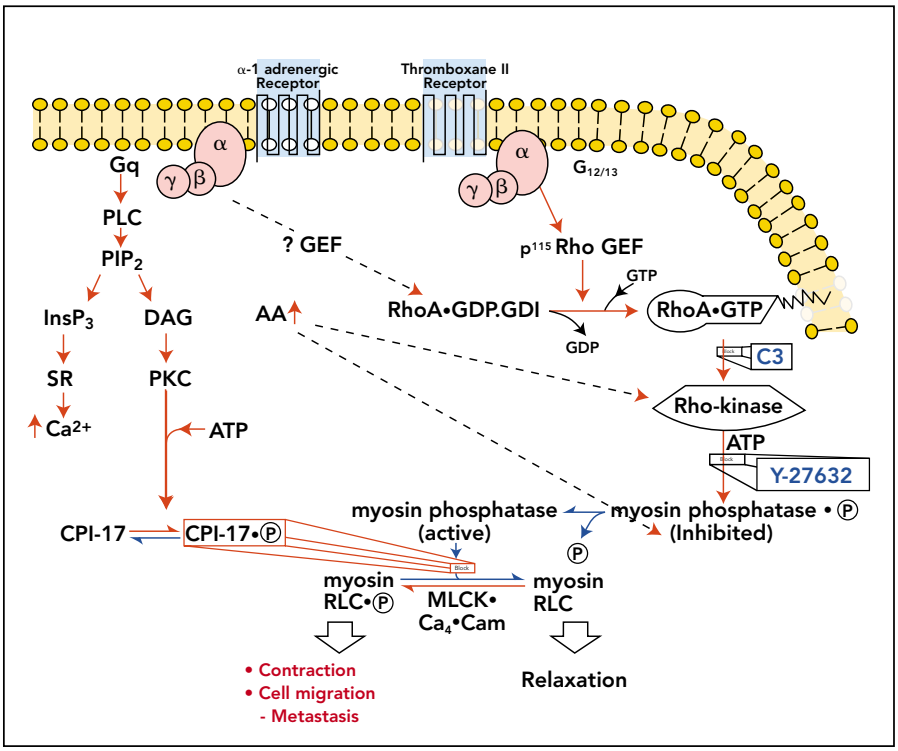


Figure 3. *Biochemistry of myosin, the Rho kinase pathway, and maintenance of tone. Myosin light-chain kinase (MLCK), acting through Ca^{+2} and calmodulin (Ca_4CaM), is responsible for phosphorylation of myosin. Phosphorylated myosin interacts with actin to increase smooth muscle tone. This maintains the penis in a detumescent state. Conversely, myosin phosphatase (MP) dephosphorylates myosin to reduce tone. Rho kinase, in combination with ATP, prevents phosphorylation of MP, thereby maintaining the latter molecule in the inactive state. Thus, constant tone is maintained even in the absence of NE. This may explain how the penis is kept in the detumescent state. Rho kinase inhibitors in vivo and in vitro relax cavernous smooth muscle, raise intracavernous pressure, and trigger penile erection. A variety of signal transduction pathways (shown) are responsible for maintaining a constitutive increase in Rho kinase. Gq, G-protein; PLC, phospholipase C; PiP_2, inositol biphosphate; DAG, diacyl glycerate; SR, sarcoplasmic reticulum; PKC, protein kinase C; GEF, guanine nucleotide exchange factor; Aa, arachadonic acid; RLC, regulatory light chain; GDP, guanidine diphosphate; Y-27632, selective inhibitor of Rho kinase. Reproduced from Somlyo and Somlyo,[16] with permission from the publisher, Cambridge University Press.*

Ca^{+2}.[15] Following activation of G-protein-coupled receptors such as the α_1-adrenergic receptor, membrane-associated phospholipase C forms diacylglycerate (DAG) and inositol triphosphate (IP3). IP3 triggers release of Ca^{+2} from sarcoplasmic reticulum, thereby raising cytosolic Ca^{+2}. The binding of Ca^{+2} to calmodulin mediates smooth muscle contraction through activation of myosin light chain kinase (MLCK) (Figure 3).[16] MLCK phosphorylates myosin heads, which allows interaction of actin and myosin. This interaction can be conceptualized as crossbridge formation that enables smooth muscle contraction and maintains force. In the penis this translates into detumescence. Conversely, phosphatases and myosin phosphatase (MP) drive this reaction in the opposite direction, resulting in smooth muscle relaxation. Recently, MP activity has been used as a target to induce penile erection. MP is regulated by cytosolic Rho kinase.[16] Phosphorylation of MP by Rho kinase maintains myosin light chain phosphatase (MLCP)[17,18] in its inactive state. However, inhibition of Rho kinase allows dephosphorylation of MP, prevents intrinsic contractile tone, and allows relaxation of cavernous smooth muscle.[16] The net effect is penile erection in vivo, which occurs even after blockade of L-arginine/NO/cGMP pathways. These recent observations raise the issue of whether penile erection is an active event or merely a case of NO's overriding a constant Rho-kinase-mediated smooth muscle tone.

In summary, four general schemes underlie pharmacological strategies for treatment of ED. Agents that 1) raise cGMP, 2) raise cAMP, 3) prevent IP3 formation, or 4) inhibit Rho kinase can initiate or facilitate penile erection. The first three mechanisms form the basis of current pharmacological therapies. The fourth mechanism offers a potential new strategy. In addition, genetic methods that result in expression of maxi-K channels or nNOS have been used experimentally to improve erectile function in animal models of aging with diabetes.[19]

Pathophysiology Pertinent to Pharmacologic Treatment

The ideal therapy for ED should reverse or reduce the processes leading to corpus cavernosal smooth muscle dysfunction or lack of cavernous nerve activity. ED is often due to the inability of cavernous smooth muscle to relax. Events that prevent relaxation include nerve damage, endothelial dysfunction, or alterations in receptors or signal transduction pathways in cavernous smooth muscle. In general, patients with ED respond well to pharmacologic therapies. Only 10%–15% of men with ED fail to respond to currently available drugs.[20–22] Failures could derive from either a loss in smooth muscle content or interruption of signal transduction pathways. Pathophysiology often changes in the L-arginine/NO/cGMP system. Aging is associated with ED. Lower mRNA for nNOS is found in older than in younger animals.[23] Likewise, the endothelial-mediated relaxation of corpus cavernosum is

reduced in older animals. Whether these changes are due to aging independent of neural or vascular pathology is unclear.

Up to 60% of men with diabetes mellitus have ED.[24] Cavernous smooth muscle from diabetic men with ED exhibits a reduction in endothelium-dependent relaxation.[25] In diabetic models, penile nitric oxide synthase (NOS) activity and content are reduced.[26] ED may be the result of glycosylation end products or of the interaction between NO and free radicals to form peroxynitrite. Atherosclerosis and elevated cholesterol are significant risk factors for ED.[27] Like hyperglycemia, hypercholesterolemia impairs endothelium-mediated relaxation. Experimentally, exogenous L-arginine improves this endothelial defect.[28] In an animal model of atherosclerotic ED, obstruction of iliac arteries impairs cavernous relaxation and downregulates nNOS.[29] Smoking, injury, and castrate levels of testosterone are also associated with a decrease in penile NOS activity or content in animal models.[30,31] Hence, a disruption of the L-arginine/NO/cGMP pathway may occur in many diseases linked to ED. PDE-5 inhibitors that amplify the NOS pathway, such as sildenafil, appear to be effective in these disorders.

Table 1
Classifications of Drugs for Erectile Dysfunction

Pharmacological type
Phosphodiesterase (PDE) inhibitors
Nonselective (papaverine)
PDE-5-selective (sildenafil, tadalafil, vardenafil)
α-Adrenergic-receptor antagonists
Nonselective α_1/α_2 (phentolamine)
α1-selective (moxisylyte)
Adenylate cyclase activators (VIP, CGRP, forskolin, PGE_1)
NO donors (linsinomine)
K channel openers
Dopamine agonists
Nonselective D_1/D_2 (apomorphine)
Selective D_2 (sumanitrole)
Serotonergic (mCPP, trazodone)
Melanocortin agonists (melanotan II)
Opiate antagonists (naltrexone)

Route of Administration
Intracavernous
Topical/intraurethral
Oral

Type and Site of Action		
	Initiator	Conditioner
Central nervous system	Apomorphine Melanocortin agonists	Testosterone Naltrexone
Peripheral nervous system or smooth muscle	PGE1 VIP, CGRP Linsinomine	Phentolamine Sildenafil, tadalafil, vardenafil

Drugs for the Treatment of ED

Classification of Drugs

Table 1 provides a list of drugs for treatment of ED, by pharmacologic type, route of administration, and type and site of action.

Intracavernous/topical/intraurethral agents. Intracavernous agents used to treat ED are peripheral initiators. Papaverine is a nonselective phosphodiesterase inhibitor. Phentolamine is a competitive α-adrenergic-receptor antagonist with affinity for α_1- and α_2-adrenergic receptors.[13] This drug can also block serotonin (5-HT) and inhibit release of histamine from mast cells.[5] Intracavernous papaverine has been used alone to achieve erections. In contrast, α-adrenergic-receptor antagonists achieve greater benefit when combined with papaverine and/or prostaglandin E_1 (PGE_1). Thymoxamine (moxisylyte) is a relatively selective α_1-adrenergic receptor antagonist. In addition, thymoxamine possesses some minor antihistamine activity. Thymoxamine has shown to produce erections of moderate quality when injected intracavernously in double-blind crossover studies.[32] The main advantage of this particular agent is safety. In comparison to papaverine, moxisylyte tends to cause less fibrosis and less-prolonged erections.[33] Prostaglandin E_1 administered intracavernously, either alone or in combination with other drugs, is the most common drug used by this route. Between 40% and 70% of patients with ED respond to intra-

cavernous injection of PGE_1.[34] The drug acts through P-receptor stimulation. It is metabolized in the penis to PGE_0, which is also biologically active. The actions of PGE_1 and PGE_0 are mediated by adenylate cyclase, which causes a rise in cAMP. PGE_1 alone is more effective than moxisylyte alone (71% vs 50% responders). PGE_1 can be effective in men with severe vasculogenic impotence.

The combination of PGE_1 with S-nitrosoglutathione (SNO-GLU) had some degree of synergy, but it is unclear whether this represents greater efficacy than that of PGE_1 alone.[35] As mentioned previously, VIP is released from parasympathetic nerves within the penis. Like PGE_1, intracavernous VIP stimulates adenylate cyclase production, causing penile erection.[5] VIP as a single agent results in poor-quality erections. However, when it is combined with papaverine and phentolamine, the triple drug mixture is effective in over 81% of patients. This VIP/phentolamine/papaverine mixture is reported to cause less penile pain, fibrosis, or priapism than phentolamine or papaverine alone.[22] A two-drug mixture of VIP and phentolamine has also been used therapeutically.

Calcitonin gene-related peptide (CGRP) is found within afferent nerves of the penis. Intracavernous CGRP also raises cAMP and produces penile erection.[36] However, minimal clinical data are available.

Linsidomine chlorohydrate is an NO donor. Along with sodium nitroprusside, it has been injected intracavernously and found to produce penile erection.[37] However, some contradicting reports have been published. Sodium nitroprusside has been associated with severe hypotension when given intracavernously.

Oral/sublingual agents. Oral agents of dubious effectiveness have been used for decades in the treatment of ED. Among the earliest drugs used was yohimbine, an α_2-adrenergic-receptor antagonist. Yohimbine possesses little efficacy for the treatment of ED.[38]

Oral agents of dubious effectiveness have been used for decades in the treatment of ED.

Phentolamine has had mixed results when given orally to treat ED.[13] Initial clinical trials failed to show any significant efficacy. However, with a reformulated preparation enabling rapid onset, phentolamine demonstrated some efficacy over placebo in patients with mild to moderate ED.[3] It is unclear whether this agent will be resurrected for FDA approval for treatment of ED within the United States.

Chronic injection of narcotics leads to decreased libido and impotence. Thus, it is not surprising that sporadic reports suggest that opiate receptor antagonists, such as naloxone or naltrexone, demonstrate some usefulness for ED. Two small studies with naloxone, only one of which was placebo controlled, noted a small increase in sexual performance.[5] In two randomized placebo-controlled studies, naltrexone was shown to increase early morning erections or enhance sexual activity.[39,40]

Similar contradictory results have been seen with the use of the atypical antidepressant trazodone. Trazodone may work primarily through its metabolic by-product, meta-chlorophenyl piperazine (mCPP). mCPP is a 5-HT_{2C} receptor agonist. Trazodone in open-label trials showed some efficacy in sexual performance.[41] However, when placebo-controlled clinical trials were performed, little if any improvement in erectile function or sexual performance was documented.[42] Regardless, trazodone enhances the duration of nocturnal erections. Thus, this agent may be useful not to treat sexual dysfunction but as an alternative for antidepressant-induced ED.

The most important advance in the treatment of ED has been the development of oral PDE-5 inhibitors. This class of drug is exemplified by sildenafil. Interestingly, caffeine is a weak PDE-5 inhibitor. Anecdotal reports even suggest caffeine improves erectile function.[43] Sildenafil and other PDE-5 inhibitors inhibit PDE-5 at very low concentrations. Sildenafil and two agents currently in phase II clinical trials, vardenafil and tadalafil, inhibit PDE-5 at different concentrations (Table 2).[11] Sildenafil and vardenafil bind to cGMP, thereby blocking the PDE-5–mediated catalytic mechanism that dephosphorylates and breaks down cGMP. In contrast, tadalafil is structurally distinct from sildenafil and vardenafil and may inhibit PDE-5 by a slightly different mechanism. Selectivity for the different PDEs varies among these three agents. Vardenafil has the highest selectivity for PDE-5. Subtle pharmacokinetic differences in PDE-5 inhibitors may influence clinical use, yet efficacy is likely to be very similar among these drugs. The efficacy of PDE-5 inhibitors varies from 40% to 85% depending on the severity

Anecdotal reports even suggest caffeine improves erectile function.

and etiology of ED.[21] As the mechanism of the PDE-5 inhibitor class requires sufficient NO release mediated through sexual stimulation, it is not surprising that there is a "learning" effect in some patients who are reinitiating sexual activity; although about two thirds of patients respond within the first two doses, the rest only begin to respond on subsequent dosing reaching a maximum threshold of response for the study population after about 6–8 doses.[44]

Within the central nervous system (CNS), activation of certain neural networks is associated with increased sexual activity and penile erections (Figure 4). Dopamine in certain regions within the CNS facilitates penile erections. Dopamine acts at D_1 and D_2 receptors. Activation of D_1 receptors on γ-aminobutyric acid (GABA) neurons inhibits sexual activity. Conversely, activation of D_2 receptors is associated with initiation of penile erection. Thus, it is not surprising that early findings on the D_2 agonist quinelorane showed promise in primates for treating disorders associated with reduced libido and ED.[45] However, this agent failed to progress beyond early phase II clinical trials. Anecdotal reports that dopamine agonists used to treat Parkinson's disease also increased penile erections eventually led to clinical trials with the D_1/D_2 agonist apomorphine SL for the treatment of ED. Because of side effects such as nausea when taken orally, apomorphine was reformulated into a sublingual preparation, allowing a lower dose, which is associated with much less nausea. Clinical trials revealed that apomorphine possesses greater efficacy than placebo in men with ED.[46] However, apomorphine has been approved for treating ED only in Europe.

Other substances that work within the CNS, such as melanocortin agonists, have been reported to increase nocturnal erections and those achieved by visual sexual stimuli.[47] Melanotan II awaits filing with the FDA. Other drugs that have either been considered or had clinical trials initiated include the 5-HT_{2C} agonist mCPP, the D_2 agonist sumanitrole, and oxytocin. Efficacy data are unavailable for these drugs.

Table 2
Pharmacologic Properties of PDE-5 Inhibitors

	PDE-5 IC_{50} (nM)	t_{max} (hr)	$t_{1/2}$ (hr)
Sildenafil	3.90	1.00–2.00	4.00
Tadalafil	1.05	2.33	17.50
Vardenafil	0.70	0.25–3.00	4.50–4.80

The PDE-5 inhibitors sildenafil, vardenafil, and tadalafil differ in selectivity, as documented by their 50% inhibitory concentrations (IC_{50}s); times to onset of action (t_{max}); and different windows of opportunity, based on their half-lives ($t_{1/2}$). For example, the long half-life of tadalafil may allow a longer window of opportunity, but also my complicate dosing instructions. However, it is important to recognize that differences in these pharmacological properties may not translate into differences in efficacy, patient acceptance, or direct extrapolation to time of onset or duration of action.

Unpublished, personal data.

Chemoprevention

In addition to treatment of ED with pharmacological therapy, another strategy is chemoprevention. Preliminary trials in diabetics with poorly controlled blood glucose levels have been undertaken with a protein kinase C β (PKC-β) inhibitor, LY333531. This agent prevents endothelial dysfunction associated with hyperglycemia and is currently in trials for diabetic retinopathy prevention. Free radical scavengers, NO substrates, direct

Main Points

- Erectile dysfunction (ED) afflicts as many as 30 million men in the United States.
- Many men do not respond to sildenafil; lack of efficacy is a much more common reason for discontinuation than side effects.
- Nitric oxide (NO) is the most important of the neurotransmitters released by the cavernous nerves that relax cavernous smooth muscle, triggering penile erection.
- ED is significantly more common in men with diabetes, atherosclerosis, or high cholesterol; smoking, injury, and castrate levels of testosterone are also risk factors.
- Many types of drugs, including phosphodiesterase (PDE) inhibitors, α-adrenergic receptors, and adenylate cyclase activators, have been used to treat ED, with varying degrees of success.
- Drugs under development for ED include free radical scavengers, NO substrates, direct activators of guanylate cyclase, Rho kinase inhibitors, and fusion compounds.

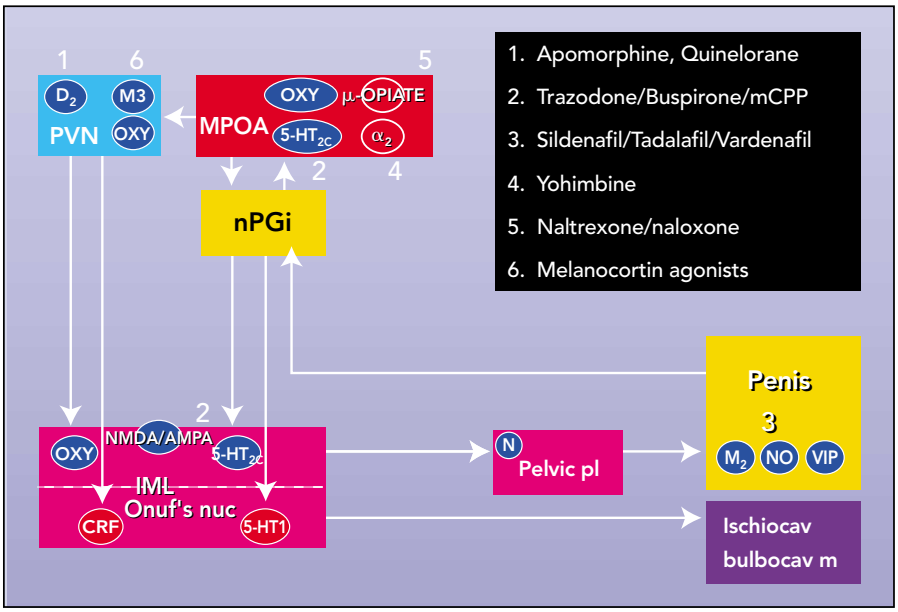


Figure 4. *Sites of action of agents associated with increased erectile function. Drugs may act through the peripheral or the central nervous system to achieve penile erection. Ascending and descending excitatory pathways responsible for penile erections rely on glutamate. Glutamate acts through N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors both in the brain and in the spinal cord. Descending neural input from brain inhibits erections mediated by serotonin (5-HT) and originates in the nucleus paragigantocellularis (nPGi). However, some serotonergic agents may facilitate erectile function. Trazodone acts in the periphery as a weak α-adrenergic-receptor antagonist and in the central nervous system as an α-adrenergic-receptor agonist at 5-HT$_{2C}$ receptors via meta-chlorophenyl piperazine (mCPP). Agents that influence preganglionic neurons in the intermediolateral (IML) cell column of the sacral spinal cord influence erections. The paraventricular nucleus (PVN) in the brain is the site of action of oxytocin (OXY) and dopamine (D). Apomorphine and quinelorane act at D-receptors within the brain to help initiate penile erection. Melanocortins act at M3 receptors to influence penile erections, possibly by the actions of D or OXY. More rostral brain centers, such as the medial preoptic area (MPOA), influence the PVN as well as the nPGi regions. Yohimbine acts rostrally to the PVN at α$_2$-adrenal receptors to facilitate erections in some species.*

activators of guanylate cyclase, Rho kinase inhibitors, and fusion compounds (eg, nitrate donor/α-adrenergic-receptor antagonists) are other types of drugs in various stages of development for treating ED.

Summary

The pharmacology of cavernous smooth muscle and the effects of drugs acting within the CNS that influence sexual behavior are an expanding area of basic and clinical research. Substances that relax cavernous smooth muscle are potentially useful as intracavernous and occasionally oral therapies for ED. These drugs rely on mechanisms that reduce cytosolic Ca^{+2}. Substances that increase copulatory behavior in animals may also be useful, but their transition into clinical use has been rare. In the near future, attempts to increase the bioavailability, reduce the side effects, and increase the specificity of PDE-5 inhibitors may prove of clinical benefit, provided that they are accompanied by improvements in efficacy in the more difficult to treat ED patients. Combination strategies using different classes of drugs are appealing but potentially entail the risk of priapism and other cumulative side effects, and may simply be economically prohibitive. Drugs acting within the CNS may have a particular use in altering libido and thus indirectly enhancing erectile function. Despite such advances, one limitation of traditional pharmacology is the demonstration that many disorders and aging are associated with loss of cavernous smooth muscle, possibly due to apoptosis. Therefore, in the long term, molecular manipulation of receptors, signal transduction molecules, ion channels, or smooth muscle growth may be fruitful tactics to enhance erectile function. ■

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Summary of Discussion Following Dr. Steers's Presentation

Dr. Steers summed up the salient point of his presentation as these: First, current pharmacologic therapy is primarily based on peripheral mechanisms, and future agents may be acting with the central nervous system. Second, combination therapy may someday be exploited in certain patient groups to enhance efficacy.

Dr. McCullough protested, "But clearly it's going to have to be a single formulation. The more complicated we make the song and dance around creating the erection, the less likely it is that the patient is going to pursue that form of therapy." Steers agreed, but countered that if the patient is not satisfied with the results of a single formulation, he might take the combination to "get something done." The paradigm for such combination therapy, Steers said, would be anti-hypertensive and anti-depressive therapy. Currently only a third of hypertensive patients are adequately controlled with monotherapy. In the motivated patient for whom one drug is not working, there would be a high motivation for combined therapy.

It is important, Steers continued, to not forget financial issues. Combining two different agents with a comparable pricing scheme today would result in a cost of $40 or $50 for an erection. That might, he said, be a good reason to combine agents.