Oral Pharmacotherapy to Manage Erectile Dysfunction in Spinal Cord-Injured Men

Angelo E. Gousse, Marie-May Lambert, and Robert R. Kester

Background: Until recently, approved available treatments for neurogenic sexual disorders related to spinal cord injury (SCI) included intracavernosal injection or intraurethral delivery of vasoactive agents such as PGE1, alprostadil, vacuum constriction devices, and surgical implantation of penile prosthetic devices. Improved understanding of penile physiology led to the development of sildenafil as the first oral pharmacotherapeutic agent available to successfully treat erectile dysfunction (ED) in men with SCI. Materials and Method: We reviewed the current English literature related to oral pharmacotherapy to treat ED in men with SCI including emerging oral agents that have yet to be tested in the SCI population. Results: Sildenafil is the most extensively studied oral agent to treat ED in spinal cord-injured patients. The results are invariably favorable, and the drug is safe in men with SCI T5 and above. Emerging agents, including sublingual apomorphine and vardenafil, have yet to be adequately studied in the SCI population. Conclusion: Clinicians caring for spinal cord-injured patients should remain informed of the current developments in oral pharmacotherapy of ED in men with SCI. Prospective, randomized trials involving a large number of participants with SCI should be encouraged to objectively measure the merit and safety of these emerging oral erectogenic agents in this patient population. Key words: *apomorphine, erectile dysfunction, phosphodiesterase inhibitor, sildenafil, spinal cord injury*

Until recently, approved available treatments for neurogenic sexual disorders related to spinal cord injury (SCI) included intracavernosal injection or intraurethral delivery of vasoactive agents such as PGE1, alprostadil, vacuum constriction devices, and surgical implantation of penile prosthetic devices.[1] For many years, clinicians had hoped for the development of effective oral pharmacotherapy in the management of erectile dysfunction (ED) in men with SCI. An oral agent to treat ED would be ideal, because men with SCI would feel more self-sufficient and would be more likely to take advantage of a noninvasive therapy that would not require any manual dexterity and would be more spontaneous than previously available options.

Over the past 10 years, significant strides have been made in the understanding of the pathophysiology of ED, and this has led to the emergence of three oral agents[2]: (a) the least efficacious, yohimbine; (b) apomorphine, currently being introduced in Europe; and (3) sildenafil, currently the most efficacious and widespread agent. Although sildenafil is the only oral agent that has been extensively studied in men with SCI, there is reason to believe that others will follow in the

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near future. Because many basic science investigations to elucidate the pathophysiology of ED are ongoing,[3] the future is promising for the development of oral pharmacotherapy to treat ED in men with SCI. An understanding of the physiology and pathophysiology of erection is necessary to explain the mechanism of action of the current and potential future oral agents.

Physiology of Erection

Physiology of erection involves various neurotransmitter systems in the central nervous system (CNS) and peripheral nervous system, as well as peripherally in the penis itself.[4] Although much progress has been made in the understanding of CNS control of penile erection, oral pharmacotherapy is currently at its infancy. Penile erections occur via sensory-mediated pathways (reflexogenic-mediated erection) and/or by CNS-mediated pathways (psychogenic-mediated erection). Sensory pathways by tactile manipulation via dorsal nerve of the penis utilize both somatic and automatic afferents that include pro-erectile pathways via the pudendal nerve.

The penile nerves terminate in the medial portion of the dorsal horn and in the central gray matter. In the CNS, involvement of the several structures has been demonstrated in the forebrain. At the level of the forebrain, the medial amygdala and the medial preoptic area (MPOA) have been implicated in erectile physiology.[5,6] In the hypothalamus, important erectile centers have been labeled by retrograde techniques as well by c-fos expression after nerve stimulation.[7]

Several investigators have proposed that MPOA of the hypothalamus may be an integration site for the central control of erection. Within the MOPA, alpha-2 adrenergic receptor-mediated inhibitory pathways and dopaminergic-mediated pro-erectile pathways appear to be important. Hence, dopaminergic agonists (such as apomorphine) or alpha-2 adrenergic receptor-mediated antagonists (such as yohimbine) have been found to have a role in the treatment of ED.[8]

The paraventricular nucleus, which receives neural input from the MPOA, is also located in the hypothalamus and is believed to have a pro-erectile role, potentially through oxytocin-dependent pathways. Although the mechanism remains unclear at the level of the medulla and the pons, Barrington's nucleus appears to play a role in regulation of erection as demonstrated by retrograde labeling studies.[9] Serotonergic pathways are thought to mediate the inhibitory pathways in the brainstem. Thus, serotonin reuptake inhibitors are used for the treatment of premature ejaculation.[10]

Innervation of the erectile bodies is well established. The peripheral nerve supply to the penis occurs via sympathetic (T11-L2), parasympathetic (S2-S4), and somatic (S2-S4) nerve fibers. In general, the parasympathetic and somatic innervations provide pro-erectogenic pathways, whereas sympathetic innervation provides inhibitory erectile pathways.[11] Consequently, the level of SCI dictates the clinical presentation. For instance, an upper SCI may have a different presentation from a lower SCI and may benefit from different treatment modalities.

There are two main pathways by which axons can reach the penis: (a) prevertebral pathway, including the lumbar splanchnic, hypogastric, and cavernosal nerves and the caudal mesenteric; and (b) paravertebral pathway leaving the spinal column at the sacral level to the pelvic plexus. This latter

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structure is particularly important because iatrogenic injury during radical retropubic prostatectomy or pelvic trauma can cause ED. Furthermore, it should also be noted that the serotonergic 5-HT-2c receptors in the spinal cord could play a pro-erectogenic role.[12] This accounts for part of the mechanism of action of the antidepressant trazodone, which yields an active metabolite that is a potent activator of 5-HT-2c receptors. Although trazodone is known to cause priapism, Enzlin et al.[12] found that trazodone 200 mg/day had no effect on sexual function in men with ED without major organic findings.

Penile anatomy is well established. The penis is composed of three bodies of erectile tissue: the corpus spongiosum encompassing the urethra and terminating in the glans penis, and the two corpora cavernosa, which function as blood-filled chambers providing structure to the erect organ. The corpus cavernosum is a unique vascular bed consisting of sinuses whose arterial blood supply arises from the resistant helicine arterioles that, in turn, are fed from the deep penile cavernosal artery. The trabeculae are drained by the emissary venules that communicate with the cavernosal veins. The trabeculae, while arterially fed, have measured blood Po_2 of 20–40 mm Hg when the penis is in the flaccid state.

Penile erection is the end result of smooth muscle relaxation. Cavernosal smooth muscle relaxation is processed by cholinergic nonadrenergic, noncholinergic (NANC) neurotransmitters such as nitrous oxide (NO), vasoactive intestinal peptide (VIP), and possibly calcitonin gene-related peptide (CGRP)-containing nerves.[11] NO and NANC nerves are believed to mediate dilation of the helicine arterioles as well as the trabecular smooth muscle via cyclic guanosine monophosphate (cGMP)-dependent and independent pathways.[13] The influx of arterial blood is associated with a rise in blood Po_2 (90–100 mm Hg). Shear stress and acetylcholine receptors on the trabecular endothelium elevate intracellular calcium that in turn stimulates more production of NO. NO easily diffuses into the smooth muscle, resulting in relaxation.

As the trabecular sinuses relax and fill with blood, intracavernosal pressure and volume increase. Veno-occlusion develops through stretching and compressive forces exerted by expandable trabecular tissue of the tunica albuginea and subtunical venules. VIP- and CGRP–mediated pathways that proceed through cyclic adenosine monophosphate cAMP-dependent pathways may further contribute to trabecular smooth muscle relaxation. Prostaglandin E (PGE) is synthesized by the corpus cavernosum smooth muscle cells and binds to specific PDE (EP) receptor on the smooth muscle that can increase intracellular cAMP levels and further potentiate smooth muscle relaxation. Research continues to elucidate other receptors and potential pathways for mediating trabecular smooth muscle tone.[14]

Mechanism of Action of Sildenafil

The mechanism of action of sildenafil is well established. The oral agent acts by way of a selective inhibition of the cGMP catabolism by blocking phosphodiesterase type 5 that is responsible for degradation of cGMP. This leads to an amplification in the cGMP concentration that finally enhances the intensity and duration of penile erection.[14] For this reason, it is expected that in the absence of any sexual stimuli sildenafil would not cause

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It can be expected that, at least in SCI patients with preservation of the conus medullaris, sildenafil may enhance penile erection either after local perineal or penile stimulation via the sacral spinal parasympathetic reflex arc and/or after central psychogenic excitation transmitted from the brain to the intact, centrally connected sacral spinal cord.

erection in men with ED of either organic or psychogenic etiology.

Sildenafil and SCI patients

Sildenafil is the first and only oral agent to be extensively studied and clinically evaluated in men and women with SCI.[15–20] In able-bodied adult men, sensory input from the genitals is transmitted to the brain to allow perception of erection. Higher CNS activity enhances or inhibits reflex activity from the sacral segments.[18] Neurogenic ED is a very well-established complication in men with SCI of different levels and severity. Patients with upper motor neuron (UMN) SCI, that is, above the sacral spinal cord, usually preserve reflexive erections. However, most of them do not achieve sufficient rigid erections to permit successful sexual intercourse, because reflexive penile reaction to somesthetic contact stimuli often is of too short a duration.

This observation indicates that pathways other than those of reflexogenic origin may be necessary to potentiate an erection satisfactory for intercourse.[19] It has been shown that many such patients may benefit from sildenafil oral therapy.[20] In contrast, after lower motor neuron (LMN) paraplegia, sacral reflexes from the perineal area are lost and the perception of erection as well as the effect of higher CNS activity on penile response is no longer transmitted. Therefore, the ability to reach penile tumescence becomes completely abolished and sildenafil is useless, unless it can be demonstrated that the thoracolumbar pathway has any functional compensatory role in mediating erotically (noncontact) provoked erections.[20]

An understanding of the neuropathophysiology of spinal cord-injured men is important to predict the therapeutic response to sildenafil. Accordingly, it can be expected that, at least in SCI patients with preservation of the conus medullaris, sildenafil may enhance penile erection either after local perineal or penile stimulation via the sacral spinal parasympathetic reflex arc and/or after central psychogenic excitation transmitted from the brain to the intact, centrally connected sacral spinal cord. Schmid et al.[20] found, in accordance with the mode of action of sildenafil, a high response rate in SCI patients with a preserved spinal sacral erection center. However, a clear enhancement of the erections after sildenafil intake could also be observed in patients with complete destruction of the conus/cauda equina but preserved thoracolumbar segments and an absence of reflexic but presence of psychogenic erection, presumably via sympathetic channels. These results are in contrast with previous reports that only attribute an inhibitory effect to the sympathetic pathways,[11] because a clear excitatory pathway must be present. Additionally, Courtois et al.[21] recently confirmed that men with LMN lesions are able to maintain their psychogenic erection capacity.

Animal studies also support this finding. In some animal reports, stimulation of the

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penile nerves failed to elicit penile responses[22,23] or elicited only a few responses after stimulation of the distal portion of the nerves.[24] Hypogastric stimulation has also been shown to increase penile pressure in rats with chronic interruption of the sacral parasympathetic outflow. Observations from men with SCI who lost reflex activity from the external genital area show that many of them still have erections elicited by supraspinal erotic stimuli. Because innervation of the male reproductive system involves two neural pathways (sacral and thoracolumbar), it is presumed that the thoracolumbar pathway is operant in cases of low SCI.[20]

Experimental data indicate that the hypogastric nerve (HGN) pathways mediate psychogenic erection in men with SCI. However, the importance of the HGN pathways in mediating erection in neurologically intact men remains poorly understood. Furthermore, animal researchers have proposed that neural plasticity may enable or potentiate an erectile function for the HGN nerve that may be absent or minimally operant before spinal trauma.[25] Regardless, the clinical implication is that patients with LMN lesions should not be considered as irreversibly impotent and should not be denied a trial of sildenafil treatment.

Schmid et al.[20] found that both types of patients (UMN, LMN) might profit from sildenafil, because they have preserved at least one spinal erection center and the dose required to obtain sufficient erection to permit sexual intercourse does not appear to vary between patients with UMN or LMN. In contrast, destruction of both centers impaired treatment success, as it could be shown in two of the nonresponders. In these cases, the neuronal impulses that are required to initiate normal erections after having started the enzymatic cascade in the corpora cavernosa were completely absent, and treatment with sildenafil consequently failed. This situation is not different from that after a complete peripheral denervation of the corpora cavernosa after a nonnerve-sparing radical prostatectomy.[26]

The titration study performed by Schmid et al.[20] confirmed that most SCI patients needed a dose of 50 mg of sildenafil. There was a tendency for higher dosage in cases with complete SCI in comparison with cases of incomplete SCI, as well as in patients with urodynamic cystometric curves consistent with LMN injuries compared to patients with UMN ones.

Clinical usage of sildenafil

Several authors have investigated the clinical usage of sildenafil in men with SCI. Schmid et al.[20] conducted a study to evaluate the efficacy and safety of sildenafil in the treatment of SCI patients with ED. Moreover, they looked for neurological conditions permitting therapeutic success and for the ideal dose needed to achieve sufficient erections. In that study, 41 SCI patients were prospectively examined. Sexual dysfunction was assessed by means of the International Index of Erectile Function (IIEF) questionnaire and neurological examination. Psychogenic erection capacity was tested by audiovisual stimulation and reflexive erection was tested by using a vibrator device. Neurophysiological recordings and urodynamic cystometrogram were performed in parallel to clinical examinations. Neurophysiological recordings included sympathetic skin responses (SSR), pudendal somatosensory evoked potentials (pSSEP), and bulbocavernous reflex (BCR). Urodynamics was aimed at classifying the

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neurogenic bladder dysfunction (UMN vs. LMN). Intracavernous injection tests with PGE1 were performed in all patients to exclude major organic disease. Then, 50-mg sildenafil was first given three times. Thereafter, the doses were adapted according to patients' reports.

Clinically, 28 participants preserved either reflexive erections or psychogenic erections, 11 had both types, and only 2 presented with a complete loss of erection. There were 38 patients (93%) who had a positive response to sildenafil and reached a penile rigidity sufficient to permit sexual intercourse. Nearly 10% (4/41) suffered from side effects such as headache or dizziness. Two participants stopped therapy because of side effects. At least 36 patients (88%) continued treatment with sildenafil. The authors found sildenafil to be a valuable and safe therapeutic management in ED of SCI patients. The most common dose required to achieve a satisfying erection was 50 mg. Patients with vasculogenic ED were nonresponders to sildenafil. The study supported the hypothesis that proposes that the efficacy of sildenafil depends on either sacral (S2-S4) or thoracolumbar (T10-L2) spinal segments being spared; these segments have been shown to be of relevance in mediating psychogenic erections in male SCI patients. Complete disturbance of any neurogenic impulses excludes successful treatment.

Derry et al.[27] were among the first to study the efficacy and safety of oral sildenafil in men with ED caused by SCI. They evaluated the efficacy and safety of 50-mg doses of sildenafil during a 28-day period in patients with ED caused by SCI (cord level range, T6 through L5). Patients with SCI at or above T5 level were excluded. The study was double-blind and placebo controlled, and all patients had to be able to achieve at least a partial reflexogenic erectile response to penile vibratory stimulation. No patients discontinued treatment due to adverse events. The authors concluded that oral sildenafil, taken as required (not more than once daily), significantly improves the quality of erections and satisfaction with sex life in men with ED caused by a SCI between T6 and L5.

Giuliano et al.[28] for the Sildenafil Study Group reported favorable results on a randomized trial of sildenafil for the treatment of ED in SCI. Of 143 men with residual erectile function at baseline, 111 (78%) reported improved erections and preferred sildenafil to placebo. The authors found oral sildenafil to be an effective and well-tolerated treatment for ED caused by SCI. These findings were confirmed by Sanchez Ramos et al.[29] and Gans et al.[30]

Green and Martin[31] reported on the clinical assessment of sildenafil in the treatment of neurogenic male sexual dysfunction after the initial "hype" that followed the release of the drug. The group from the Shepherd Center, Atlanta, Georgia, evaluated the efficacy and safety of sildenafil over a 2-year period in patients with ED caused by SCI and multiple sclerosis in a clinical practice after Food and Drug Administration (FDA) approval and release of the medication to the general health care community. Study design included 40 patients; 33 patients had SCI (13 tetraplegics, 20 paraplegics; 14 complete, 19 incomplete) and 7 patients had MS. All patients were prescribed sildenafil in varying dosages to achieve erections sufficient for sexual intercourse. The authors concluded that sildenafil was a safe and effective first-line treatment for the treatment of male neurogenic ED. However, they cautioned that close clinical surveillance was necessary so

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that patients can avail themselves of other options should sildenafil not be effective.

Effect of sildenafil on quality of life

Hultling et al.[32] evaluated quality of life (QoL) in 178 patients with SCI who were receiving sildenafil for the treatment of ED. The study was a multicenter, randomized, double-blind, placebo-controlled, flexible-dose, two-way crossover study conducted between June 1996 and January 1997. Study centers were in Australia, Belgium, France, Germany, Norway, Sweden, and the United Kingdom. Questions 13 and 14 of the 15-item IIEF addressed QoL issues directly related to ED in these 178 men with SCI. A five-item questionnaire that addressed concerns that men had about their erection problems was also used to evaluate the impact of ED on QoL. Several commonly used psychometric instruments, including the Medical Outcomes Survey (MOS) Short Form-12, Psychological General Well-Being Index, and MOS Family Survey, assessed general QoL issues. Significant improvements were seen for overall satisfaction with sex life (IIEF Q13), sexual relationship with partner (IIEF Q14), and concerns about erectile problems ($p < .0001$). Improvements were reported in scores for the generic QoL parameters of mental health, well-being, depression, and anxiety ($p < .05$, sildenafil vs. placebo). The authors demonstrated that treatment with sildenafil can significantly improve key QoL parameters in men with ED caused by SCI.

Safety of sildenafil

Sildenafil is absolutely contraindicated in SCI patients who are using prescribed or recreational organic nitrates. The use of sildenafil in patients with cardiac disease who are not currently taking nitrates is controversial and warrants substantial caution. High-risk patients include patients older than 65 and those with hepatic and renal impairment. Patients with retinal disorders, such as retinitis pigmentosa and macular degeneration, may also have adverse effects to sildenafil.

Several authors have reported on the safety profile of sildenafil in men with SCI. It is noteworthy that Derry et al.[27] excluded SCI patients at or above T5 level. However, only 2 of 12 such patients experienced adverse events; none of the events was severe enough to cause discontinuation of the oral agent. Schmid et al.[20] included patients with SCI from C4 to L5 and even to the level of the conus and cauda equina in their series. They only had two withdrawals due to side effects. Their percentage of drug-related side effects (10%) was comparable to that of previous studies, and the side effects were usually mild in severity. Consistent with other reports,[27–31] the main adverse events were identical to those in non-SCI patients and included headache, flushing, dizziness, dyspepsia, and blurred vision. None of their patients had reported symptoms of autonomous dysreflexia and none had priapism. Thus, to date, there is no data in the literature to indicate that SCI patients with levels of injury higher than T5 are more prone to sildenafil-induced adverse side effects.

Apomorphine

Apomorphine was first produced by the treatment of morphine with acid. This resulted in a different molecular structure without narcotic properties but with modest sedative effects. Although it was initially synthesized in the United Kingdom more

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than 100 years ago, its erectogenic properties were not noticed until the 1970s, and this was a purely serendipitous finding.[6] It has been used either orally or subcutaneously, but, because of its adverse profile (particularly gastrointestinal upset), it remained only a pharmacologic curiosity in sexual medicine. Modification of the preparation and the use of sublingual route have largely circumvented the undesirable effects while preserving the pro-erection properties. Apomorphine sublingual (SL) is marketed in Europe under the proprietary name Uprima. The compound is a dopaminergic agonist with affinity for dopamine receptors, mostly D2. Within the brain, D2 is known to be involved in sexual function. Apomorphine induces selective activation in the nucleus paraventricularis leading to erectogenic signals.

In the study by Altwein et al.,[33] more than 5,000 men participated in phase II/III clinical trials to assess the safety and efficacy of apomorphine SL doses ranging from 2 to 6 mg. The most favorable risk/benefit ratio was seen with the dose optimization regimen of 2–3 mg. The 3-mg dose provided efficacy comparable to that of 4 mg but with fewer side effects. The primary endpoint was the percentage of successful attempts with erections rigid enough for intercourse; this was one of the most objective endpoints in ED trials to date. Information obtained from validated questionnaires completed by the participants and their partners revealed that the proportion of attempts resulting in erections firm enough for intercourse was 49.4% with 3 mg compared to the baseline value of 24.3%. Erections occurred between 18 and 19 minutes after taking apomorphine SL 2 or 3 mg. The most common side effect was nausea, which decreased with continued use. Vasovagal syncope was reported in <0.2% of men and was preceded by clear prodromal symptoms.

The successful, sublingual use of the D1/D2 receptor agonist apomorphine for the treatment of erectile dysfunction strongly supports the belief in the participation of the dopaminergic system in the control of sexual function.

Recently, the cardiovascular safety profile of apomorphine SL in patients on stable doses of oral antihypertensive agents and nitrates was evaluated.[34] The only potentially clinically significant interaction between apomorphine SL and antihypertensive agents or short-acting nitrates was greater orthostatic decreases in systolic blood pressure in the alpha-blocker and calcium channel blocker groups. The most common adverse events in the apomorphine SL group were dizziness, nausea, and headache. It was concluded that patients who received common antihypertensive agents and short-acting nitrates in conjunction with apomorphine SL (even at higher than recommended doses) had no clinically significant changes in heart rate or blood pressure greater than changes that were seen with apomorphine SL alone.

A recent investigation from Giuliano et al.[35] demonstrated the existence of a spinal site of action of the drug in addition to the brain. Dopamine immunoreactive fibers have been found in the thoracolumbar sympathetic and, to a lesser extent, in the lumbosacral parasympathetic nucleus. The clinical significance of

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these investigative findings remains to be determined. In another report, these same authors reviewed the role of dopamine receptors and sexual function.[36] The successful, sublingual use of the D1/D2 receptor agonist apomorphine for the treatment of ED strongly supports the belief in the participation of the dopaminergic system in the control of sexual function. However, the exact involvement of dopamine in sexual motivation and in the control of genital arousal in men with SCI remains unknown.

Dula et al.[37,38] from the Apomorphine Study Group and Altwein et al.[33] from Germany reported that apomorphine SL is an effective, well-tolerated drug for ED in able-bodied men. To date, there has been no prospective clinical trial using apomorphine SL in men with SCI.

Yohimbine

Although yohimbine was available for the treatment of ED many years before the advent of sildenafil, little is known about the clinical performance of the drug. Tam et al.[39] reviewed the literature and analyzed the clinical, pharmacological, and therapeutic profiles of yohimbine relevant to its potential utility in the management of patients with ED. The authors found that relatively few well-designed studies have been completed. From these, however, it can be concluded that yohimbine as monotherapy possesses only modest efficacy in ED patients. Overall, the benefit-risk profile of this drug would indicate that it has potential in the treatment of ED, more probably as part of a combination strategy (e.g., with a drug that enhances the NO pathway). These conclusions do not necessarily apply to men with SCI, because yohimbine has not been studied in this patient population.

Other Potential Agents Under Development

Sildenafil citrate is a relatively poorly selective PDE5 inhibitor that potentiates the accumulation of cGMP resulting in smooth muscle relaxation of the cavernosal erectile bodies. The PDE5 inhibition approach is also being used in the investigational drug IC351, which is in the later stages of phase III clinical trials. This PDE5 inhibitor is reported to be more selective than sildenafil citrate and have no vision PDE6 side effects and a longer half-life.[6]

Another investigational PDE5 inhibitor, BAY 38-9456 (vardenafil), is also undergoing clinical trials, and its clinical value has been published recently.[40] The treatments were well tolerated, although slightly more adverse events, primarily headache, flushing, and nasal congestion, were seen with the 40-mg dose compared with placebo. The findings confirm that vardenafil is able to generate stronger erections of longer duration than placebo under conditions of visual sexual stimulation in able-bodied patients with ED. Although several other PDE5 inhibitors are in various stages of development, none has been studied in men with SCI.

Alpha blockers have also been explored as a treatment for ED since the early studies of Brindley with intracavernosal phenoxybenzamine.[41] Recently, this area has been revisited. Oral phentolamine has been explored as a noninvasive pharmacotherapy for ED and is in its late stage of clinical trials.[42] However, oral alpha blockers alone have not been as efficacious as other medications.

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Tamsulosin, an alpha blocker used to treat lower urinary tract symptoms, has been noted to improve sexual function ancillary to treatment of voiding dysfunction.[43] Alpha blockade alone may not be sufficient to induce erection, but this therapy may be useful in combination with other agents or for the treatment of milder cases of ED. Studies to evaluate the value of alpha blockers to treat ED in men with SCI are not currently available.

The Future

Although the future is difficult to predict, two new PDE5 inhibitors, as well as sublingual apomorphine and phentolamine, will most likely come before FDA approval in the next 2–3 years. The availability of these oral agents will allow for increased noninvasive therapy. Because these drugs work through different pharmacologic mechanisms, combination or augmentation therapies may be necessary to achieve optimal clinical results. However, these must be approached with caution due to potential drug interactions. Several agents are currently in late phase III development.[44]

Vardenafil (Bayer, New Haven, CT), a PDE5 inhibitor, and the combination of yohimbine and L-arginine (NitroMed, Boston, MA) are in early phase III development. Early clinical and preclinical studies are investigating new phosphodiesterase inhibitors, cyclic AMP activators, alpha-adrenergic antagonists, dopamine agonists, melanocyte-stimulating hormone, potassium channel modulators, endothelin antagonists, and new NO donors. Continued research in the field of ED and penile physiology is likely to uncover other penile-selective vasodilatory pathways that could yield a new generation of selective and efficacious oral pharmacotherapeutic regimens.

Oral agents will remain attractive in the management of men with SCI with ED, because they permit discrete administration and are less invasive than the non-oral agents. They make possible a more appropriate and natural sexual activity in men with SCI, which leads to a high degree of acceptance. Furthermore, the fact that the current oral medications are simple to take and present few side effects contributes to their high acceptance and low attrition rate. Clinicians caring for spinal cord-injured patients should remain informed of the current developments in oral pharmacotherapy of ED in men with SCI. Prospective, randomized trials involving large number of SCI participants should be encouraged to objectively measure the merit and safety of these emerging oral erectogenic agents in this patient population.

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