Introduction

Erectile dysfunction (ED) is the inability to achieve and maintain an erection for satisfactory completion of sexual intercourse. While prevalence estimates vary, data from the National Health and Nutrition Examination Survey (NHANES) suggest overall prevalence in the US adult male population to be 18.4% (1). Worldwide, large-scale studies estimate overall prevalence in a similar range, between 10% and 20% (2).

The aetiology of ED is multifactorial and may be related to any functional disturbance along the pathway from higher cortical structures to molecular effectors mediating smooth muscle relaxation in the helicine arteries. ED can be caused by psychogenic, endocrine, neurogenic, iatrogenic and vascular phenomena. Risk factors for ED include diabetes mellitus, obesity, high blood pressure, heart and vascular disease, the metabolic syndrome, smoking and benign prostatic hyperplasia. ED is strongly positively correlated with age, with a disease burden of 5.1%, 14.8%, 43.8% and 70.2% in men aged 20–39, 40–59, 60–69 and 70+ years respectively (1). Vascular disease is also highly associated with ED, and in the NHANES analysis, the age-adjusted prevalence of ED was 27.7% in men treated for hypertension and 38.6% in men with diabetes mellitus (1). ED may also be iatrogenic, as may be the case (3) with radical pelvic surgery or medication (4). Common medical culprits of ED include thiazides, beta-blockers, antidepressants and hormonal drugs (4,5).

The first line therapy for ED is phosphodiesterase type 5 inhibitors (PDE5i). Additional therapies include intracavernosal injections of vasoactive
agents, vacuum erection devices (VED), urethral suppositories and penile prostheses. PDE5i ease-of-use and its highly favourable side effect profile, compared with those alternatives en vogue only a decade ago, make treatment with this class very attractive (6–12). However, according to the Global Better Sex Survey, which included 12,563 individuals worldwide, only 7% of respondents with ED reported actually using prescription ED medication, whereas 74% were willing to use prescription ED medication (13). Even in the absence of ED, 68% of healthy men would be willing to use prescription ED medication if they thought it would make sex better, and 64% of partners would support such a decision (13,14). In spite of ostensible zeal, approximately half of individuals discontinue use of PDE5i beyond 1 year (12,13,15,16). The mismatch between these data and actual long-term adherence patterns is magnified when one examines special populations with associated comorbidities, such as diabetes mellitus, hypertension, cardiovascular disease and prior prostatectomy (17,18).

Optimising response is paramount, as ED can negatively impact not only patients’ sexual satisfaction, self-esteem and quality of life, but it may also cause psychological and emotional turmoil for both partners (13,19–22).

The goal of the current review is to highlight opportunities for improving PDE5i long-term adherence and results. We begin with a discussion of currently available and upcoming PDE5i, their individual pharmacokinetic characteristics and preferences between them, and offer comparisons of novel treatment regimens. Finally, we discuss long-term adherence patterns, review published data and propose patient, patient-partner and provider-centred opportunities for improvement.

**Physiology of erection and mechanism of action**

An erection is a neurovascular response, and includes arterial dilatation, trabecular smooth muscle relaxation and activation of the corporeal veno-occlusive mechanism (23). These vascular responses are initiated by adrenergic, cholinergic, and nonadrenergic-noncholinergic (NANC) effector systems (24). Cavernosal smooth muscle tone controls penile flaccidity and rigidity. In the absence of stimulation, the sympathetic nervous system and tonic adrenergic discharge maintain contraction of the cavernous smooth muscle and helicine resistance arterioles to maintain penile flaccidity (24). With sexual stimulation, the parasympathetic nervous system via NANC nerve terminals is activated. The release of NO from these neurons in response to sexual arousal causes vascular smooth muscle relaxation (24). Enhanced parasympathetic input reinforces this response, with increased acetylcholine release and augmented NO release from endothelial cells lining the helicine arterioles (25). NO is the critical physiologic mediator of cavernosal vasorelaxation despite evidence that other vasodilators are involved in the erectile response, including vasoactive intestinal peptide, prostaglandins and acetylcholine (24–27). The elevated levels of NO activate soluble guanylyl cyclase (sGC) in the smooth muscle cell, which converts guanosine triphosphate into cyclic-guanosine monophosphate (cGMP) (28). An increase in cGMP stimulates protein kinase G to phosphorylate potassium and calcium channels, causing a decrease in cytosolic calcium, dilation of the helicine arterioles and relaxation of trabecular smooth muscle (28). Increasing intracavernosal volume and pressure expands the sinusoidal spaces against the tunica albuginea and traps blood by compressing the subtunical venular plexus and emissary veins; thereby, maintaining erection (24,28). The degradation of cGMP by PDE5 is the pivotal reaction in terminating the above cascade. Accordingly, inhibition of PDE5 potentiates the erectile response in the presence of adequate sexual stimulation (24,29).

**PDE5 inhibition and side effect profile**

There are 11 types of PDE enzymes, all of which function in the degradation of cyclic adenosine monophosphate to adenosine monophosphate and cGMP to GMP (30,31). PDE enzymes are widely distributed throughout the body, with varying activity in different tissues (30). PDE5 is found in the smooth muscle of the corpus cavernosum, skeletal muscle, vascular and visceral smooth muscle, cerebellar and pancreatic tissue, platelets, kidneys and lungs (32). Other isozymes, such as PDE1, found in the heart, PDE6 in the retina and PDE11 in skeletal muscle, may be inadvertently inhibited via drug action and may lead to unintended drug reactions (33). For example, inhibition of PDE6, involved in retinal phototransduction, is responsible for blue vision, or cyanopsia (33,34). Adverse effects most often reported with the use of PDE5i medications are: headache (33), flushing, dyspepsia, nasal congestion, visual disturbance and myalgia (35–37). Visual disturbances are almost exclusively associated with sildenafil, and back pain with tadalafil.

While the vast majority of side effects seem to be benign, evidenced by tens of millions of prescriptions dispensed worldwide, there have been reports of some exceedingly rare, however, potentially very
adverse effects associated with PDE5i use. There have been reports of seizures, migraine and other neurological changes; however, there are no large, well-controlled studies to equate this association (38,39). In rat models, PDE5i cause a decreased cerebrovascular response to hyperoxia, but not normoxia, which is associated with hyperexcitability and increased seizure activity. This mechanism cannot be generalised to humans, and the stability in normoxic conditions make it less appealing as a causal explanation (40). Tadalafil was shown to cause electroencephalogram changes 2 h after oral dosing in 12 of 35 patients and 48 h after oral dosing in two of 35 patients (41). While these studies show PDE5i have some effect on the brain, it is clear that additional studies need to be performed to elucidate the mechanism and exact effect.

In addition to neurological changes, PDE5i have been associated with sensory toxicities (38). The most frequent, serious disorder associated with PDE5i use is nonarteritic ischemic optic neuritis (NAION), which may result in irreversible blindness (42). Whether PDE5i are actually responsible for NAION remains questionable, with only individual cases or small studies linking the two (43) and a number of larger studies finding no association (44,45). The effect of PDE5i on the auditory system has recently garnered attention as well. The Food and Drug Administration (FDA) has reported 29 cases or small studies linking the two (43) and a number of larger studies finding no association (44,45). The effect of PDE5i on the auditory system has an expected onset of action of 30 min with estimated maximum effect at 1 h and a total duration of effect of 4–6 h (50). Sildenafil potency, measured by the concentration at which 50% of PDE5 enzyme is inhibited (IC50), has been reported to be 3.9 nmol/l (50–53). In the blood, approximately 96% of sildenafil is protein-bound with the peak serum concentration (Cmax) of 440 ng/ml being reached at a median time of 60 min (Tmax range 30–120 min) following a 100-mg oral dose (29). In geriatric patients (>65 years of age) or patients with hepatic impairment or severe renal insufficiency [creatinine clearance (CrCl) <30 ml/min], there are observed increases in serum concentrations because of decreased excretion in addition to altered protein binding (50). Sildenafil is a lipophilic molecule; thus, dosing close to consumption of a fatty meal can reduce absorption and drug effect. Sildenafil is metabolised both in the liver, by the P-450 enzymes CYP3A4 (major) and CYP2C9 (minor), and in the gut wall. As a result, sildenafil’s oral bioavailability is only 38–41% (29).

Vardenafil
Vardenafil (Levitra™; Bayer Healthcare Pharmaceuticals, Leverkusen, Germany), the second PDE5i to be approved in the U.S., was designed specifically as a treatment for ED. Vardenafil is the only PDE5i medication to be approved in both film-coated tablet and orodispersible tablet (ODT) forms. Vardenafil differs from sildenafil in both its selectivity and its pharmacokinetics. Vardenafil has selectivity for PDE5, i.e. >15 times greater than for PDE6, >130 times greater than for PDE1, >300 times greater than for PDE11 and >1000 times greater than for PDE2, 3, 4, 7, 8, 9, 10 (54). Vardenafil is rapidly absorbed, with detectable plasma levels 8–18 min after dosing and peak plasma concentrations noted between 15 min and 3 h (median 0.7 h for 20 and 40-mg dose, 0.9 h for 10-mg dose) (55). The duration of effect for vardenafil is 5–7 h and the manufacturer recommends taking the medication 30 min to 1 h before intercourse to achieve maximum effect (56).
Vardenafil potency, measured by the concentration at which 50% of PDE5 enzyme is inhibited (IC50) is reported at 0.1–0.7 nmol/l (51,52,55). Bioavailability of vardenafil is reported to be relatively low (approximately 15%) because of a large effect of gut wall and first-pass hepatic metabolism (36,57). In plasma, 93–95% of the drug is protein-bound and the estimated volume of distribution is large, indicating wide distribution of the drug throughout the body. Vardenafil is largely metabolised in the liver by the P-450 enzymes CYP3A4 (major) and CYP2C (minor) (57). Geriatric patients with moderate and severe renal insufficiency (CrCl < 50 ml/min), and patients with hepatic impairment display altered pharmacokinetics and should be started on a lower dose than the general population (36). Unlike sildenafil, vardenafil’s pharmacokinetics are not greatly affected by concomitant consumption of fatty foods (36). Vardenafil use is not recommended for patients who take type-1A or type-3 antiarrhythmics or in patients with congenital prolonged QT interval (variably defined, with QTc of ≥ 450 ms consider prolonged) syndrome (54).

**Tadalafil**

Tadalafil (Cialis®; Eli Lilly, Indianapolis, IN) is a very selective PDE5 inhibitor that was initially developed as a prospective treatment for cardiovascular disease. Tadalafil’s structure is markedly different from that of either sildenafil or vardenafil, reflected by its pharmacokinetics (32,51,58). Tadalafil’s selectivity for PDE5 is > 700 times greater than for PDE6, > 10,000 times greater than for PDE1-4 and 7–10 and > 5 times greater than for PDE11 (59,60). Tadalafil’s onset of action is estimated to be 20 min after oral dosing with duration of effect between 24 and 36 h (51,53). The manufacturer recommends oral dosing 2 h prior to intercourse to achieve maximum effect (32). Tadalafil potency, measured by the concentration at which 50% of PDE5 enzyme is inhibited (IC50) is 0.94 nmol/l (51,52). In plasma, tadalafil is 94% protein-bound with peak plasma concentrations, measured at 322 ng/ml, measured at a median time after oral dosing of 120 h (range 30–360 min). Unlike sildenafil or vardenafil, tadalafil absorption is unaffected by food or alcohol consumption (58). At least 36% of a tadalafil oral dose becomes bioavailable, although at this time absolute bioavailability has not been reported (36). Tadalafil is metabolised in the liver by P-450 enzyme CYP3A4. There were no observed differences in tadalafil metabolism in the geriatric population vs. the general population (36). Tadalafil has not been studied in patients with severe hepatic impairment, but patients with mild-moderate impairment showed similar pharmacokinetics to the general population. Of note, although tadalafil is not renally excreted, a series of acute dose pharmacokinetics studies in patients with impaired renal function showed an increased incidence of myalgia, the drug’s most common adverse side effect (61). It has been proposed that patients with diminished renal function have an altered hepatic cytochrome system and that this may be responsible for the altered metabolism (38). Therefore, a 5-mg starting dose is recommended in patients with moderate renal insufficiency and should be the maximum dose given to patients with end-stage renal disease (36).

**Avanafil**

Avanafil (Stendra™; VIVUS, Inc., Mountain View, CA) is highly selective, has a rapid onset of action, and is the newest PDE5i to be approved for use in the United States (62). Studies have demonstrated avanafil has high selectivity for PDE5 and against other PDE isozymes, particularly PDE1, 6 and 11 (63,64). Peak response to avanafil occurs 20–40 min after oral dosing (65). Avanafil reaches a peak plasma concentration at 34 min after oral dosing and has a half-life (t1/2) of 1.23 h (66). Avanafil potency, measured by the concentration at which 50% of PDE5 enzyme is inhibited (IC50) is 5.2 nmol/l (67). Like the other PDE5i medications, avanafil is metabolised by the P-450 system in the liver (68).

**PDE5i in development**

In addition to the medications that have been approved for use in the United States, there are a number of PDE5i medications currently in development or being used in other countries. For those with such data available, we discuss here their pharmacokinetics, efficacy and tolerability. We limit the scope of this discussion to those in phase II clinical trials or beyond.

Udenafil (Zydena®; Dong-A Pharmaceutical Co., Ltd, Seoul, South Korea), approved in South Korea since 2005 and in the Russian Federation since 2008, has a long 1/2 of 11–13 h and rapidly reaches peak plasma concentration (tmax, 1–1.5 h) (69). In phase III trials, udenafil improved erectile function (EF) in men with ED of various aetiologies (69,70). It had similar adverse effects to the rest of the class with no serious adverse events reported (69). Udenafil showed efficacy in men with comorbid diabetes mellitus, independent of haemoglobin A1c levels, which may support the use of the drug in diabetic men (71). Two phase III, randomised, placebo-controlled trials enrolling 618 and 601 men completed in March and April of 2010, respectively, showed efficacy and improved satisfaction in men dosed with 50, 100, or...
150 mg udenafil compared with placebo (72). These results have not yet been discussed in a peer-reviewed publication.

Mirodenafil is a PDE5i that was approved for ED treatment in South Korea in 2007. It was investigated in a multicentre, double-blind, placebo-controlled trial enrolling 223 men with various ED aetiologies, which showed improved scores on the International Index of Erectile Function (IIEF) Erectile Function domain (IIEF-EF), on diary-recorded Sexual Encounter Profile (SEP) penetration success (SEP2) and maintenance of erections (SEP3) during intercourse, as well as on the global assessment questionnaire (GAQ) and a life satisfaction assessment (69). Adverse effects were similar to those occurring with other medications in its class. No visual disturbances or serious adverse events were reported (69). There does not appear to be a major pharmacokinetic advantage for this drug over currently available PDE5i, and there are no ongoing studies listed on ClinicalTrials.gov as of this writing.

Lodenafil carbonate, developed in Brazil, is a PDE5i with a unique chemical structure. It consists of two molecules of lodenafil linked by a carbonate bridge that degrades after ingestion, releasing active lodenafil (73). Lodenafil has a $T_{\text{max}}$ of 80 min and 1/2 of 2.4 h (73). While the elimination time is at the shorter end of the spectrum, it is not as brief as that of avanafil. It was evaluated in a phase II trial that included 60 men treated with lodenafil 20, 40 and 80 mg doses compared with placebo. While there were improvements in IIEF-EF, SEP2 and SEP3, the IIEF-EF only increased with statistical significance in the 80-mg group relative to placebo (74). Adverse effects noted were typical for its class; however, visual disturbances were reported, and further trials are needed to further characterise these findings (74). One trial investigating efficacy and safety of lodenafil in men with ED and comorbid diabetes mellitus has been completed, but no results were yet available at the time of writing (72).

SLx-2101 (Surface Logic, Inc., Brighton, MA) is a PDE5i, i.e. currently under development. SLx-2101 is particularly interesting because it is metabolised to an active metabolite, SLx-2081 (75). The benefit of SLx-2101 is its long duration, which is caused by its pharmacokinetics, the long 1/2 and activity of its metabolite. SLx-2101 has a 1/2 of 8–13 h and $T_{\text{max}}$ of 1 h, whereas SLx-2081 has a 1/2 of 9–14 h and $T_{\text{max}}$ of 2.8 h (76,77). Noted side effects have been minimal, consisting mainly of headache, with visual effects occurring at an 80-mg dose (76). Studies evaluating the efficacy of SLx-2101 are ongoing, but initial results suggest it is safe and long lasting (77). There are no investigations in men with ED currently being conducted or registered on ClinicalTrials.gov at the time of writing.

### PDE5i efficacy and tolerability

#### Sildenafil

As one of the most widely distributed drugs in history, sildenafil has demonstrated safety and efficacy. The first analysis of sildenafil in humans was reported in 1996, treating 12 men with ED without an organic cause (79,80). Sildenafil use increased duration of rigidity, total number of erections and improved erectile activity compared to placebo. The landmark follow-up study of 861 men with a combination of organic (70%), psychogenic (18%) and mixed ED by Goldstein et al. (81) confirmed sildenafil’s potential, reporting improved EF after 24 weeks in 56, 77 and 84% of men taking sildenafil 25, 50 and 100 mg respectively. EF was evaluated via the IIEF, a patient log and a global-efficacy question. A second, flexible, dose-escalation branch was
performed that allowed for dosing adjustments over a 12-week period. Seventy per cent of men were taking sildenafil 100 mg and reporting improved erections at the end of 12 weeks, compared to 19% of controls. The most marked side effects reported were headache (32%), flushing (21%), dyspepsia (17%), rhinitis (12%) and visual disturbances (10%). It should be noted that despite these adverse effects, 92% of men completed the 32-week extension study. This trial demonstrated that sildenafil was safe and efficacious, vastly improving upon contemporary treatments for ED. In addition to its sexual benefits, Muller et al. (82) studied changes in relationship quality, citing improvement in categories, such as quarrelling, tenderness and togetherness in an observational study of 105 men treated with sildenafil. The global scientific community followed these successes with continued validation of the drug’s efficacy (80,83–85) and tolerability (86).

Vardenafil

Vardenafil is another successful drug that has been widely used by men all over the world. As a review, preliminary studies of vardenafil in humans by Stark et al. (87) and Klotz et al. (55) demonstrated efficacy, and the first in-home large-scale trial of 601 men randomised to 5, 10 and 20 mg doses showed improved EF measured by IIEF at all doses compared to placebo (88). Hellstrom et al. conducted a major study demonstrating sustained efficacy and tolerability in 805 men with mild, moderate and severe ED (89,90). The authors demonstrated improvements compared to placebo in all primary outcomes, including the IIEF-EF, diary-recorded SEP2 (penetration success) and SEP3 (maintenance of erections) during intercourse. Vardenafil also restored normal EF in 89% of men with mild ED and 39% of men with severe ED (89). In light of these data, the FDA approved vardenafil in August of 2003 and follow-up studies have demonstrated sustained efficacy and tolerability (91).

The ODT formulation was approved 23 June 2010 and has become more prominent within the ED treatment landscape (92). The ODT formulation has been shown to be safe, efficacious and fast acting (93). Data from a multicentre phase III trial of vardenafil 10 mg ODT was included in a post hoc integrated analysis that assessed changes in SEP3 and number of intercourse attempts at 15-, 30- and 60-min intervals. Patients taking vardenafil 10 mg ODT had a 62.5% positive response to SEP3 vs. 29% in the placebo group (94). Reduced spontaneity is a criticism of on-demand treatment regimens; however, the fast therapeutic onset demonstrated by these data may assuage those concerns.

As discussed previously, vardenafil has greater potency and selectivity for PDE5 than sildenafil, allowing for smaller dosages. While the side effect profile was similar to sildenafil, neither the study by Porst et al. nor that by Hellstrom et al. reported any significant changes in colour vision, a finding congruent with the selectivity profile of the drug for primarily PDE5, 1 and 3 (88,89).

Tadalafil

Before its November 2003 FDA approval, tadalafil was studied in seven randomised, multicentre, double-blind, placebo-controlled trials involving over 4000 subjects (95–97). The endpoints measured in these studies were similar to prior PDE5i investigations and included the IIEF-EF domain score, SEP2 and SEP3. The studies all demonstrated improvement in the three primary endpoints compared to placebo. Seftel (98) showed efficacy of the 20-mg dose to placebo, and Porst and colleagues demonstrated an increase in successful intercourse attempts

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at 24 and 36 h after dosing (59). A large-scale study of 1112 men by Brock et al. (97), which integrated work from five sites, demonstrated dose-dependent improvements in each of the endpoints. Long-term efficacy and tolerability was demonstrated in an 18–24 month open-label extension trial involving 1173 men taking tadalafil 5, 10, or 20 mg (95). Most commonly reported treatment emergent adverse events (TEAEs) were headache (15.8%), dyspepsia (11.8%), nasopharyngitis (11.4%) and back pain (8.2%). Only 6.3% of patients discontinued treatment because of TEAEs in the 18- to 24-month study. The profile was similar to that reported in the prior trial by Porst et al. (59), which included headache (14%), flushing (10%), dyspepsia (5.1%) and myalgia (6%). This side effect profile is common to the PDE5i class, although a clear etiology for myalgia and back pain has not been delineated and occurs with higher frequency in tadalafil users (95,99). Given these data, tadalafil represents a compelling alternative to sildenafil. It is not associated with vision changes, and because of its long half-life, it has no requirement to be taken 1 h before intercourse.

Avanafil
The FDA approved Avanafil (Stendra) on 27 April 2012 after three randomised, double-blind, placebo-controlled, parallel group clinical trials demonstrated safety and efficacy with step-wise dosing at 50, 100 and 200 mg (62,100). The primary endpoints were typical, including the IIEF-EF, SEP2 and SEP3. In the trial by Goldstein et al. (100) that included 646 men with ED, avanafil led to significant improvement in all three endpoints compared to placebo. Improvement in all three categories was also seen in a comparable examination of avanafil in subjects with ED population (38,104–106), and 30–40% of initial responders are not satisfied with on-demand treatment even after restoration of EF (107). Factors associated with non-response to PDE5 are condition severity, medications, incorrect usage and comorbidities such as diabetes mellitus, vascular disease, radiotherapy for prostate cancer, hypogonadism, psychosocial factors and neurological damage (102,103). Capable comparisons of the individual utility of each drug for these specific conditions can be found elsewhere.

Initial response to PDE5i is 60–70% in the general ED population (38,104–106), and 30–40% of initial responders are not satisfied with on-demand treatment even after restoration of EF (107). As mentioned previously, more than half of individuals who initially respond to PDE5i treatment discontinue usage within 2–3 years (12,13,15,16,104,108). In an attempt to better tailor ED treatment, patient preference amongst individual PDE5i and treatment regimens should be considered. Among 52 men with ED, the relative importance of success outcomes with regard to their ED treatment were, in order of preference: cure, pleasure, partner satisfaction, reproducibility, naturalness, control, duration, spontaneity, penetration and number of sexual encounters per week (109).

A number of preference comparisons have been completed among sildenafil, vardenafil and tadalafil. Although some have been observational, sponsored by industry, or criticised for bias, they do suggest a general preference for tadalafil. The first preference comparison among PDE5i, notably sponsored by the drug maker, was an open-label crossover study of on-demand sildenafil and tadalafil in 155 men (37). They reported a 9 : 1 preference for Tadalafil in the
6-month follow-up period (37). Among sponsored studies, one showed at least 59% of patients preferred tadalafil to sildenafil (110), and two found that 66% (111) and 73% (112) of subjects preferred tadalafil to sildenafil and vardenafl (113). Of five independent comparison studies, three showed subjects preferred tadalafil to the other two drugs (3,114,115), whereas two studies (3,116) did not show a statistically significant difference among them (113). A 6-month observational cohort study found no difference in efficacy among the three drugs, but found that tadalafil users had higher scores on the time concerns domain of the Psychological and Interpersonal Relationship Scales Short Form, a finding reported in other work as well (103,117). Tadalafil users also had a relatively lower risk of changing or discontinuing treatment (117). While some of these studies have been criticised for bias or their industry sponsorship (113,118), it is notable that none has found tadalafil to be inferior with statistical significance.

**Daily dosing in the treatment of ED**

Despite better success with tadalafil on-demand compared to sildenafil and the favourable pharmacokinetic profiles of vardenafil and avanafil, the on-demand regimen in general is criticised for lacking spontaneity, naturalness, and having a less than ideal onset and duration of action (109). Men engaging in unplanned sexual activity may not have the time or desire to plan medication dosing prior to sexual activity onset, resulting in treatment failure (33). Daily dosing circumvents the requirement that drug ingestion be temporally related to sexual activity (119).

A study by McMahon (7) was among the earliest to examine the efficacy and safety of daily tadalafil in 112 men with moderate-to-severe ED, who were previous non-responders to on-demand tadalafil. Administration of daily tadalafil was associated with significant improvements in IIEF-EF and SEP3 scores compared to on-demand dosing regimens. A follow-up study, enrolling 145 men with ED irrespective of their previous treatment response, compared on-demand tadalafil 20 mg and daily tadalafil 10 mg (8). The study boasted statistically significant improvements in IIEF-EF and SEP3 in tadalafil daily compared to on-demand. The first randomised, double-blind, placebo-controlled trial of single daily dose tadalafil 5 and 10 mg compared with placebo, reported IIEF-EF scores of 9.7, 9.4 and 0.9 respectively (9). Importantly, the same group conducted an open-label extension of the above study (2008) for 1 and 2 years, and not only reaffirmed safety and efficacy, but also showed sustained improvements in measures of sexual satisfaction, including IIEF Intercourse Satisfaction, IIEF Overall Satisfaction and GAQ1 and GAQ2 scores (10). Numerous subsequent investigations have confirmed daily tadalafil to be as safe and efficacious as on-demand tadalafil (102,107,120–125).

Chronic, daily dosing is attractive because of high patient satisfaction and its potential to limit vascular stress-related endothelial damage (102,126–128). Daily PDE5i use may also lead to improvements in EF that build over time and are maintained after treatment cessation (102,126,129). Studies in men with ED who were previously unresponsive to PDE5i suggest 50% of these patients may respond to daily tadalafil (7,130,131).

Whatever the cause, tadalafil daily dosing is associated with improved EF over time. Shabsigh et al. showed that initial success predicted future success in tadalafil treatment by pooling data from two randomised trials examining reliability and efficacy of daily dose tadalafil. Following initial successful intercourse, individuals taking tadalafil had higher success rates in subsequent intercourse attempts than those taking placebo (125). Porst et al. (74) echoed that finding, and conducted a retrospective analysis examining EF following cessation of long-term daily tadalafil treatment in 158 subjects. After a 1-year treatment period, 81% of subjects had improved at least one IIEF-EF domain category. Even after treatment cessation for a 4-week period, 44.9% of subjects had improved in at least another category in EF (74). While recent study by Rubio-Aurioles et al. (132), failed to show patient preference for daily tadalafil compared to on-demand tadalafil, there was a significant difference in the time concerns domain of the Psychological and Interpersonal Relationship Scales (PAIRS) scale.

As more data become available, the benefits of PDE5i chronic dosing will become clearer. Additional investigation should be conducted because of the potential for long-term protective benefits of daily PDE5i dosing, potential positive effects on vascular remodelling, improved outcomes after long-term usage because of confidence-building, improved feelings of sexual well-being and potential advantages in special populations.

**Long-term treatment success and personalised care**

Stepping back to a discussion of this drug as a class, what are factors associated with long-term treatment success? As a clear preference for one drug or regimen has not be definitively established, we consider factors associated with long-term treatment success. Among 1567 ED patients in a non-interventional, observational study analysing factors associated with continued tadalafil usage and satisfaction, the factor...
most predictive of treatment continuation at 1 year was treatment satisfaction at 1 month (133). In a separate retrospective cohort study, the most common reasons associated with sildenafil treatment discontinuation was performance below expectations, high cost, loss of interest in sex and inconvenience in obtaining the drug (104). Other factors to consider include partner and physician-related issues.

Studies analysing treatment response, when all available PDE5i were prescribed at the same time have reported significant increases in initial rates of response and satisfaction (113,134). In an independent study of patients in a Swedish clinical practice who were prescribed all three drugs, 89% (165/186) had a positive treatment response, 76% and 81% of previous PDE5i users and PDE5i naïve subjects, respectively, tried all three drugs (113). There was no significant difference overall in preference for the long vs. short acting drug type, however, previously treated patients preferred a long-acting drug and treatment-naïve patients preferred a short-acting drug. There was no difference in the age of subjects preferring long vs. short-acting drugs, and there was no significant difference in ED aetiology between the age groups. Of note, patients with mild ED had a preference for tadalafil over the short-acting drugs, and 20% of patients requested both a short- and long-acting drug. Despite any conclusions, one might begin to draw with regard to preference; only one quarter of patients at the end of 1 year preferred the treatment they had been using when the study began. Based on these results, the authors note, if patients do not have the opportunity to test all three drugs, then 40% of patients will not be using their optimal drug combination (113).

Despite these data, an analysis of UK refill patterns indicated that, of men prescribed only one PDE5i on treatment initiation, 3.4% switched drug prescriptions, and that it was nearly four times more common to switch from tadalafil or vardenafil to another drug (135). In a similar analysis of US prescription patterns using data from the health information firm NDC-Health, men were most likely to switch from tadalafil, then vardenafil and least likely to switch from sildenafil (136). While results from these two trials suggest patients initially prescribed one drug may be less likely to switch from sildenafil than from others, it does not address satisfaction or other factors that may be related to this decision process. Furthermore, if patients are prescribed all three drugs or allowed to try all three, they will likely ultimately achieve a better result than if they are permitted only to try one.

**Patient and partner-centred variables**

Up to this point, we have focused on factors related to drug pharmacokinetics, dosing, regimens and preferences for one PDE5i over another. Perhaps, the interplay of patient-centred variables, rather than drug or class variables, are more closely linked to treatment success and adherence. It is well known that psychological, social and relationship factors play heavily into sexual satisfaction and function. Psychosocial factors may influence a patient’s decision to discontinue treatment and provide a framework to consider the patient in a context broader than simply organic dysfunction (137).

On the patient side, variables, such as performance anxiety, depression, varying arousal patterns and misaligned expectations between patient and spouse, may affect the decision to continue treatment (12). Partner-centred factors are also likely to affect sexual function and may include not being accustomed to a fully sexual relationship or concern that use of a drug during sexual activity indicates a lack of desire (137). Possible confounders include relationship quality and life stressors. Some of these barriers are likely to resolve with the resumption of optimal sexual function. For example, improved EF is positively associated with improvement in a partner’s sexual satisfaction and can lead to improvements in well-being and quality of life (13). The often-high price of PDE5i has also been shown to be a key factor in long-term treatment failure. Patients may not have time or the willingness to prioritise these drugs over other essential products.

**Personalised care: the provider and opportunities for innovation in patient-centred ED management**

As the gatekeeper of the patient’s sexual health, it is particularly important for the provider to develop a comprehensive relationship with the patient to address his unique needs and tailor his treatment regimen accordingly. While PDE5i are recognised as the first line treatment for ED, drug choice and regimen are largely left to the provider’s discretion. As the current literature does not delineate one preferred PDE5i over another, the ultimate decision of drug prescribed is largely left to physician and patient preference. It is noteworthy that as sildenafil is scheduled to lose exclusivity in June of 2013, this may significantly impact current prescribing patterns and may ultimately result in a carryover effect on other PDE5i. In addition, with the recent approval of avanafil, it will continue to be important that providers consider all treatment options and that they be available for handling modifications to treatment plans, particularly in the first 4 weeks of PDE5 use. Patient counselling and regular follow-up are correlated with better adherence and outcomes, and as discussed previously, initial treatment success is highly predictive of long-term success (16,138).
Interventions by providers to enhance education, accessibility and communication via electronic interaction may be a viable adjunct or replacement for some in-office visits. There is a trend in other sectors of medicine to adopt electronic or cloud-based communication mechanisms to minimise barriers to accessing care (139). The utilisation of mobile technologies, such as internet prescribing, smartphones and web applications, should be considered not only in light of their ability to more effectively communicate and satisfy patient concerns, but also because of their potential to reduce overall medical costs to society.

Mobile applications may include assessing daily sexual satisfaction scores, electronic diary keeping and alerting the provider to non-compliance or variation in treatment protocol. For example, in HIV patients, weekly mobile phone text messaging was associated with greater retroviral medication adherence at 1 year compared to controls (140). Just an intermittent electronic questionnaire or check-up could vastly improve patient satisfaction. In one study of patients with hypertension, electronic medication reminders improved adherence by 18% (141). While reminders are less likely to be advantageous for on-demand dosing, these tools could be useful for daily dosing regimens, and the educational potential of such applications could be utilised to improve adherence.

With cost-pressures mounting, it may be difficult for many providers to offer the attention is required in some patients to secure and maintain their comfort and satisfaction with their ED care. More progressive modes of patient communication should be considered to readily address early concerns. In a retrospective analysis of the safety of internet-based prescribing (IBP) for ED, 500 randomly selected e-medicine patient records were compared with 500 electronic charts from a traditional multispecialty primary care system. The e-medicine system was superior to the traditional medicine system on five safety endpoints and non-inferior on one. The use of the e-medicine prescribing system led to significantly more uniform questioning, history taking, physical examination, education and screening (142). Medical histories taken online were also found to be superior in an earlier retrospective IBP comparison, likely secondary to the regulatory framework and patients requesting refills were highly satisfied with the service (143,144).

Given that data suggest IBP and traditional visits may be equivalent in terms of safety, IBP may offer major advantages in terms of resource requirements, early and overall patient satisfaction and consequent long-term treatment success. These modalities offer the ability to change prescriptions quickly, and patients are no longer faced with the inconvenience of an office visit for a simple refill or change of medication type or regimen. Given the accessibility of the Internet, IBP or similar options offered by local providers may actually improve physician–patient communication. Patients may be more likely to mention concerns, discuss successes, or ask for treatment changes via their mobile phone or computer than they are to schedule and follow through with a full office visit.

Because research suggests satisfaction with treatment in the first 4 weeks is most predictive of long-term treatment success, a change in focus should be highly attractive to providers. Furthermore, from an economic perspective, the arrangement is a more cost-effective solution because low-complexity visits can be handled electronically, freeing providers for visits that are better handled in person.

Conclusion

In summary, PDE5i are a safe and effective treatment for ED in adult men. There are multiple drug options from which the provider and patient may choose to optimise the likelihood of long-term treatment success. While all approved drugs display efficacy, initial drug choice should depend on a comprehensive discussion between provider and patient. Some physicians may choose to supply more than one drug initially, as patients are likely to try all three. A follow-up appointment should be scheduled soon after initiating treatment to discuss successes or any problems encountered, as data suggest treatment success in the first month to be most predictive of success over the long term. In general, vardenafil ODT and avanafil may be more appropriate for individuals who desire rapid onset of action, but who do not wish to dose every day, and tadalafil may be more appropriate for those who prefer a longer window for successful intercourse. Sildenafil has the most available literature to date and is currently scheduled to lose patent exclusivity in June 2013. Daily dosing with tadalafil has been associated with improved EF over time and may offer additional benefits; however, additional studies are needed. The evolving medical practice landscape provides opportunity for continued innovation in ED management. Increasing patient comfort with electronic communication and mounting cost pressures may shift some components of the in-office visit to the mobile space. Internet prescribing, electronic satisfaction questionnaires, smartphones and web education offer compelling and convenient tools to increase patient–provider communication and improve long-term ED treatment success.
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