REVIEW ARTICLE

PDE5 inhibitors: considerations for preference and long-term adherence

W. B. Smith II, I. R. McCaslin, A. Gokce, S. H. Mandava, L. Trost, W. J. Hellstrom

Department of Urology, School of Medicine, Tulane University, New Orleans, LA, USA

Correspondence to:
Wayne J. G. Hellstrom, Section of Andrology, Department of Urology, Health Sciences Center, Tulane University, 1430 Tulane Avenue, SL-42, New Orleans, LA 70112, USA
Tel.: +1 504 988 3361
Fax: +1 504 988 5059
Email: whellst@tulane.edu

SUMMARY

Introduction: Erectile dysfunction (ED) is a highly prevalent condition affecting nearly one in five men worldwide. The advent of phosphodiesterase type 5 inhibitors (PDE5i) has revolutionised the ED treatment landscape and provided effective, minimally invasive therapies to restore male sexual function. **Materials and methods:** A pubmed search was performed of all English language articles from 1996 to present reviewing PDE5i, including pharmacokinetics, efficacy profiles and comparisons, where available. **Results:** Currently available PDE5i in the United States include sildenafil, vardenafil, tadalafil and avanafil, each of which has unique side effect, pharmacokinetic and outcome profiles. Sildenafil is associated with increased rate of visual changes, vardenafil with QT prolongation and tadalafil with lower back pain. Avanafil and vardenafil orodispersible tablet rapidly achieve peak plasma concentration, which results in faster onset of action, whereas tadalafil exhibits the longest half-life. First time response to PDE5i is approximately 60–70%, with no significant differences in efficacy noted among therapies. The literature does not clearly demonstrate a preference for one drug. High-treatment success rates (89%) were reported when patients were prescribed all available PDE5i. Daily dosing with tadalafil is associated with improved erectile function (EF) over time. Finally, novel modes of patient–provider interaction, including internet-based education, communication and prescribing, may also improve long-term adherence. **Conclusions:** PDE5i represent first line therapy for ED with excellent overall efficacy and satisfactory side effect profiles. Enhanced communciation, coupled with increased knowledge of drug characteristics, comparative treatment regimens and optimal prescribing patterns, offer compelling tools to improve long-term treatment success.

> **Review criteria and Message for the clinic**
> - Avanafil and vardenafil have the shortest onset of action and may be best for spontaneous sexual activity.
> - Tadalafil carries the longest half-life and may be most appropriate in those who prefer sexual preparedness for longer periods.
> - Preference:
>   - Patient preference comparisons of sildenafil, vardenafil and tadalafil did not demonstrate inferiority of tadalafil and some studies showed a tadalafil preference.
>   - Prescription data of individuals taking PDE5i suggest patients are least likely to switch from sildenafil than from tadalafil or vardenafil.
>   - Future preference comparisons should be designed as randomised, placebo-controlled trials and should include avanafil
> - Further study should be conducted to investigate the effect of enhanced patient–provider communication and the utility of electronic education and prescription modalities on long-term ED treatment success

Introduction

Erectile dysfunction (ED) is the inability to achieve or 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 equivocate 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 patients of hearing loss within 3 days of beginning therapy with a PDE5i (46). The hearing loss was generally one-sided and often associated with tinnitus, dizziness, or vertigo. One-third of those affected eventually recovered, with the other two-thirds not reporting (46). In a separate, prospective human study, 18 men using PDE5i had their hearing evaluated with audiometric testing (38,47). Middle ear pressures and frequency responses from 250 to 16,000 Hz were measured 1, 5 and 72 h after oral dose of vardenafil. Four of these men demonstrated significant hearing changes 1 h after dosing. This effect was reversible in all four men, with all recovering full function by the 72-h point (47). There has been some concern with adverse cardiovascular response to PDE5i, but no major adverse cardiac profile has emerged in any of the FDA approved drugs, even in studies with exercise testing (48,49).

Considering the large volume of prescriptions for PDE5i written every year and relatively few reported serious adverse effects, it is clear that the benefits of PDE5i far outweigh the risks for most patients. However, it is important to note that some serious adverse effects may exist and that the scientific community continues to investigate any association. Side effects unique to specific drugs or regimens are discussed later, and we now offer a description of the pharmacokinetics of drugs currently approved or in phase II trials or further.

Pharmacokinetics

Sildenafil

Sildenafil (Viagra™; Pfizer, New York, NY) was the first of the PDE5i medications to be developed (Tables 1 and 2). It is 10 times more selective for PDE5 than PDE6 and is 1000 times more selective for PDE5 than PDE2-4 (50). Orally dosed sildenafil 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 (C_{max}) of 440 ng/ml being reached at a median time of 60 min (T_{max}, 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 $\geq$ 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 min (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 ($t_{1/2}$) 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 (t_{max} 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

Table 1 Pharmacokinetic properties of currently approved phosphodiesterase type 5 inhibitor

	Sildenafil (100 mg)	Vardenafil (20 mg)	Vardenafil orodispersible tablet (10 mg) (78)	Tadalafil (20 mg)	Avanafil (100 mg)
IC50 (nmol/l)	3.9	0.1–0.7		0.94	5.2
C_{max} (ng/ml)	327 ± 236	20.9 ± 1.83	13.43	378	871
T_{max} (h)	1.16 ± 0.99	0.660	1.5 (0.5–2.5)	2.0	0.555
Bioavailability (%)	38–41	15		≥ 36	–
Duration of Action (h)	4–6	5–7		24–36	0.25–6
1/2 (h)	3.82 ± 0.84	3.94 ± 1.31	5.387	17.5	1.23
% Bound	96	95		94	–
Recommended dose time prior to intercourse (h)	1	0.5–1	1	2	0.5
Vss (L)	105	208		63	–

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_{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_{max} of 1 h, whereas SLx-2081 has a 1/2 of 9–14 h and T_{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

Table 2 Pharmacokinetic properties of phosphodiesterase type 5 inhibitor in development

	Udenafil	Lodenafil	Mirodenafil	SLx-2101	SLx-2081 (SLx-2101 metabolite)
IC50 (nmol/l)					
C_{max} (ng/ml)					
T_{max} (h)	1	1.333	1.5	1	2.8
Bioavailability (%)					
Duration of action (h)					
1/2 (h)	11–13	2.4	2.4	8–13	9–14
% Bound					
Recommended dose time prior to intercourse (h)					
Vss (L)					
Study:					

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

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 aetiology 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 comorbid diabetes mellitus (100).

Hellstrom et al. conducted a phase II study comparing safety, efficacy and time-course effect of a-vanafil 50, 100, 200 mg and sildenafil 50 mg vs. placebo. The primary endpoint, duration of ≥ 60% rigidity, was measured at an early (20–40 min), intermediate (60–80 min) and late (100–120 min) interval for each treatment arm. Avanafil effect peaked in the early interval across all dosages; the peak for sildenafil 50 mg was in the late interval. Duration of rigidity for avanafil 100 mg, the half-max dose, was superior to sildenafil 50 mg at the tip of the penis in the early interval, but inferior at the base in the late interval; there was no significant difference in duration in the middle (60–80 min) interval. Treatment with avanafil 200 mg was superior to sildenafil at the early interval for the duration of rigidity at the tip and base, but it was not significantly different from sildenafil at the middle and late

intervals. Avanafil demonstrated even more impressive results in study TA-301, which analysed success rates of sexual attempts made ≤ 15 min and > 6 h after dosage with avanafil. 66.7% and 69.4% of patients taking avanafil were successful, compared with 48.1% and 50.0% in the placebo group respectively for both (101).

The most commonly reported TEAEs across phase III trials included headache, flushing and nasal congestion, all similar in nature and severity to those seen with other PDE5i. No visual disturbances, priapism, or hearing changes have been reported with this drug. Avanafil's potency, selectivity, safety and remarkably fast onset of action make it a compelling alternative to other PDE5i utilised in the treatment of ED.

Preference among PDE5i

PDE5i are strongly preferred over other ED treatment options, including VED, intracavernosal injection and penile prostheses; oral on-demand dosing is the primary mode of treatment utilised for this class (12). 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, reproduction, 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 vardenafil (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.

References

1 Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007; **120**: 151–7.

2 Hatzichristou D, Rosen RC, Broderick G et al. Clinical evaluation and management strategy for sexual dysfunction in men and women. *J Sex Med* 2004; **1**: 49–57.

3 Sommers F, Mathers M, Klotz T, Bondarenko B, Caspers HP, Engelmann U. A comparative randomised study of maximum doses of sildenafil, tadalafil and vardenafil. *Eur Urol* 2004; **3**: 105. Abstract 410.

4 Albersen M, Shindel AW, Mwamukonda KB, Lue TF. The future is today: emerging drugs for the treatment of erectile dysfunction. *Expert Opinion Emerg Drugs* 2010; **15**: 467–80.

5 Albersen M, Shindel AW, Lue TF. Sexual dysfunction in the older man. *Reviews in Clinical Gerontology* 2009; **19**(4): 237–248.

6 Montorsi F, Salonia A, Zanoni M et al. Current status of local penile therapy. *Int J Impot Res* 2002; **14** (Suppl. 1): S70–81.

7 McMahon C. Efficacy and safety of daily tadalafil in men with erectile dysfunction previously unresponsive to on-demand tadalafil. *J Sex Med* 2004; **1**: 292–300.

8 McMahon C. Comparison of efficacy, safety, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. *J Sex Med* 2005; **2**: 415–25; discussion 25–7.

9 Porst H, Giuliano F, Glina S et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Eur Urol* 2006; **50**: 351–9.

10 Porst H, Rajfer J, Casabé A et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. *J Sex Med* 2008; **5**: 2160–9.

11 Kang DH, Lee JY, Park SY et al. Efficacy and safety of tadalafil 5 mg administered once daily in Korean men with erectile dysfunction: a prospective, multicenter study. *Korean J Urol* 2010; **51**: 647–52.

12 Hackett GI. Patient preferences in treatment of erectile dysfunction: the continuing importance of patient education. *Clin Cornerstone* 2005; **7**: 57–65.

13 Mulhall J, King R, Glina S, Hvidsten K. Importance of and satisfaction with sex among men and women worldwide: results of the global better sex survey. *J Sex Med* 2008; **5**: 788–95.

14 Eardley I, Dean J, Barnes T et al. The sexual habits of British men and women over 40 years old. *BJU Int* 2004; **93**: 563–7.

15 Conaglen HM, Conaglen JV. Couples' reasons for adherence to, or discontinuation of, PDE type 5 inhibitors for men with erectile dysfunction at 12 to 24-month follow-up after a 6-month free trial. *J Sex Med* 2012; **9**: 857–65.

16 Sadovsky R, Brock GB, Gray M et al. Optimizing treatment outcomes with phosphodiesterase type 5 inhibitors for erectile dysfunction: opening windows to enhanced sexual function and overall health. *J Am Acad Nurse Pract* 2011; **23**: 320–30.

17 Goldstein I, Kim E, Steers WD et al. Efficacy and safety of tadalafil in men with erectile dysfunction with a high prevalence of comorbid conditions: results from MOMENTUS: multiple observations in men with erectile dysfunction in National Tadalafil Study in the US. *J Sex Med* 2007; **4**: 166–75.

18 McMahon CG. Treatment of erectile dysfunction with chronic dosing of tadalafil. *Eur Urol* 2006; **50**: 215–7.

19 Chevret M, Jaudinot E, Sullivan K et al. Impact of erectile dysfunction (ED) on sexual life of female partners: assessment with the Index of Sexual Life (ISL) questionnaire. *J Sex Marital Ther* 2004; **30**: 157–72.

20 Moreira ED, Brock G, Glasser DB et al. Help-seeking behaviour for sexual problems: the global study of sexual attitudes and behaviors. *Int J Clin Pract* 2005; **59**: 6–16.

21 Guay AT, Spark RF, Bansal S et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of male sexual dysfunction: a couple's problem – 2003 update. *Endocr Pract* 2003; **9**(1): 77–95.

22 Lindau ST, Schumm LP, Laumann EO et al. A study of sexuality and health among older adults in the United States. *N Engl J Med* 2007; **357**: 762–74.

23 Lue TF, Takamura T, Schmidt RA et al. Hemodynamics of erection in the monkey. *J Urol* 1983; **130**: 1237–41.

24 Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. *J Urol* 1987; **137**: 829–36.

25 Azadzoi KM, Kim N, Brown ML et al. Endothelium-derived nitric oxide and cyclooxygenase products modulate corpus cavernosum smooth muscle tone. *J Urol* 1992; **147**: 220–5.

26 Hedlund H, Andersson KE, Fovaeus M et al. Characterization of contraction-mediating prostanoid receptors in human penile erectile tissues. *J Urol* 1989; **141**: 182–6.

27 Kim ED, McVary KT. Topical prostaglandin-E1 for the treatment of erectile dysfunction. *J Urol* 1995; **153**: 1828–30.

28 Martinez-Piñeiro L, Trigo-Rocha F, Hsu GL, Heyden von B, Lue TF, Tanagho EA. Cyclic guanosine monophosphate mediates penile erection in the rat. *Eur Urol* 1993; **24**(1): 492–9.

29 Boolell M, Allen MJ, Ballard SA et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 1996; **8**(2): 47–52.

30 Beavo JA. cGMP inhibition of heart phosphodiesterase: is it clinically relevant? *J Clin Investig* 1995; **95**: 445.

31 Butcher RW, Sutherland EW. Adenosine 3′,5′-phosphate in biological materials. I. Purification and properties of cyclic 3′,5′-nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3′,5′-phosphate in human urine. *J Biol Chem* 1962; **237**: 1244–50.

32 Mercier JL. Cialis (tadalafil) Tablets – FDA Approval Label. *NDA 21-368* 2003: 1–24.

33 Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. *BJU Int* 2005; **96**: 257–80.

34 Pfizer. *Viagra. Sildenafil citrate [package insert]*. New York, NY: Pfizer, Inc, 1998: 1–19.

35 Hellstrom WJG. Current safety and tolerability issues in men with erectile dysfunction receiving PDE5 inhibitors. *Int J Clin Pract* 2007; **61**: 1547–54.

36 Uckert S, Stief CG, Jonas U. Current and future trends in the oral pharmacotherapy of male erectile dysfunction. *Expert Opin Investig Drugs* 2003; **12**: 1521–33.

37 Ströberg P, Murphy A, Costigan T. Switching patients with erectile dysfunction from sildenafil citrate to tadalafil: results of a European multicenter, open-label study of patient preference. *Clin Ther* 2003; **25**: 2724–37.

38 Shindel AW. 2009 update on phosphodiesterase type 5 inhibitor therapy part 2: updates on optimal utilization for sexual concerns and rare toxicities in this class. *J Sex Med* 2009; **6**: 2352–64; quiz 65–6.

39 Farooq MU, Naravetla B, Moore PW et al. Role of sildenafil in neurological disorders. *Clin Neuropharmacol* 2008; **31**: 353–62.

40 Demchenko IT, Ruehle A, Allen BW et al. Phosphodiesterase-5 inhibitors oppose hyperoxic vasoconstriction and accelerate seizure development in rats exposed to hyperbaric oxygen. *J Appl Physiol* 2009; **106**: 1234–42.

41 Okuyucu EE, Guven O, Duman T et al. EEG abnormalities during treatment with tadalafil, a phosphodiesterase type 5 inhibitor. *Neurol Res* 2009; **31**: 313–5.

42 Danesh-Meyer HV, Levin LA. Erectile dysfunction drugs and risk of anterior ischaemic optic neuropathy: casual or causal association? *Br J Ophthalmol* 2007; **91**: 1551–5.

43 Thurtell MJ, Tomsak RL. Nonarteritic anterior ischemic optic neuropathy with PDE-5 inhibitors for erectile dysfunction. *Int J Impot Res* 2008; **20**: 537–43.

44 Gorkin L, Hvidsten K, Sobel RE, Siegel R. Sildenafil citrate use and the incidence of nonarteritic anterior ischemic optic neuropathy. *Int J Clin Pract* 2006; **60**: 500–3.

45 Azzouni F, Abu samra K. Are phosphodiesterase type 5 inhibitors associated with vision-threatening adverse events? A critical analysis and review of the literature. *J Sex Med* 2011; **8**(10): 2894–903.

46 United States Food and Drug Administration. Questions and answers about Viagra, Levitra, Cialis, and Revatio: possible sudden hearing loss. 2007. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109012.htm (accessed July 2012)

47 Okuyucu S, Guven OE, Akoglu E et al. Effect of phosphodiesterase-5 inhibitor on hearing. *J Laryngol Otol* 2009; **123**: 718–22.

48 Thadani U, Smith W, Nash S et al. The effect of vardenafil, a potent and highly selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction, on the cardiovascular response to exercise in patients with coronary artery disease. *J Am Coll Cardiol* 2002; **40**(11): 2006–12.

49 Nehra A. Erectile dysfunction and cardiovascular disease: efficacy and safety of phosphodiesterase type 5 inhibitors in men with both conditions. *Mayo Clinic Proc* 2009; **84**: 139–48.

50 Carter AJ, Ballard SA, Naylor AM. Effect of the selective phosphodiesterase type 5 inhibitor sildenafil on erectile dysfunction in the anesthetized dog. *J Urol* 1998; **160**: 242–6.

51 Gupta M, Kovar A, Meibohm B. The clinical pharmacokinetics of phosphodiesterase-5 inhibitors for erectile dysfunction. *J Clin Pharmacol* 2005; **45**: 987–1003.

52 Gresser U, Gleiter CH. Erectile dysfunction: comparison of efficacy and side effects of the PDE-5 inhibitors sildenafil, vardenafil and tadalafil – review of the literature. *Eur J Med Res* 2002; **7**: 435–46.

53 Dorsey P, Keel C, Klavens M, Hellstrom WJG. Phosphodiesterase type 5 (PDE5) inhibitors for the treatment of erectile dysfunction. *Expert Opin Pharmacother* 2010; **11**: 1109–22.

54 Levitra. Levitra (vardenafil HCl) Tablets – FDA Approval Label. *NDA021400* 2003: 1–26.

55 Klotz T, Sachse R, Heidrich A et al. Vardenafil increases penile rigidity and tumescence in erectile dysfunction patients: a RigiScan and pharmacokinetic study. *World J Urol* 2001; **19**(1): 32–9.

56 Levitra. *Vardenafil. HCL [package insert]*. West Haven, CT: Bayer HealthCare Pharmaceuticals, 2003: 1–26.

57 Bischoff E. Potency, selectivity, and consequences of nonselectivity of PDE inhibition. *Int J Impot Res* 2004; **16**(Suppl. 1): S11–4.

58 Bella AJ, Brock GB. Tadalafil in the treatment of erectile dysfunction. *Curr Urol Rep* 2003; **4**: 472–8.

59 Porst H, Padma-Nathan H, Giuliano F et al. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 hours after dosing: a randomized controlled trial. *Urology* 2003; **62**: 121–5.discussion 5–6.

60 Curran M, Keating G. Tadalafil. *Drugs* 2003; **63**: 2203–12.discussion 13–4.

61 Forgue ST, Phillips DL, Bedding AW et al. Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. *Br J Clin Pharmacol* 2007; **63**(1): 24–35.

62 VIVUS. Stendra (avanafil) Tablets – FDA Approval Label. 2012:1–22.

63 Jung J, Choi S, Cho SH et al. Tolerability and pharmacokinetics of avanafil, a phosphodiesterase type 5 inhibitor: a single- and multiple-dose, double-blind, randomized, placebo-controlled, dose-escalation study in healthy Korean male volunteers. *Clin Ther* 2010; **32**: 1178–87.

64 Wang R, Burnett AL, Heller WH et al. Selectivity of Avanafil, a PDE5 inhibitor for the treatment of erectile dysfunction: implications for clinical safety and improved tolerability. *J Sex Med* 2012; doi: 10.1111/j.1743-6109.2012.02822.x. [Epub ahead of print].

65 Hellstrom WJ, Freier MT, Serefoglu EC et al. A phase II, single-blind, randomized, crossover evaluation of the safety and efficacy of avanafil using visual sexual stimulation in patients with mild to moderate erectile dysfunction. *BJU Int* 2012; doi: 10.1111/j.1464-410X.2012.11267.x. [Epub ahead of print].

66 Limin M, Johnsen N, Hellstrom WJ. Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. *Expert Opin Investig Drugs* 2010; **19**: 1427–37.

67 Kotera J, Mochida H, Inoue H et al. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. *J Urol* 2012; **188**: 668–74.

68 Alwaal A, Al-Mannie R, Carrier S. Future prospects in the treatment of erectile dysfunction: focus on avanafil. *Drug Des Dev Ther* 2011; **5**: 435–43.

69 Paick J-S, Kim SW, Yang DY et al. The efficacy and safety of udenafil, a new selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction. *J Sex Med* 2008; **5**(4): 946–53.

70 Kim B-H, Lim H-S, Chung J-Y et al. Safety, tolerability and pharmacokinetics of udenafil, a novel PDE-5 inhibitor, in healthy young Korean subjects. *Br J Clin Pharmacol* 2008; **65**: 848–54.

71 Moon du G, Yang DY, Lee CH et al. A therapeutic confirmatory study to assess the safety and efficacy of Zydena (udenafil) for the treatment of erectile dysfunction in male patients with diabetes mellitus. *J Sex Med* 2011; **8**: 2048–61.

72 Search of: Udenafil 'Erectile Dysfunction' – List Results – ClinicalTrials.gov. 2012.

73 Glina S, Toscano I, Gomatzky C et al. Efficacy and tolerability of lodenafil carbonate for oral therapy in erectile dysfunction: a phase II clinical trial. *J Sex Med* 2009; **6**: 553–7.

74 Porst H, Glina S, Ralph D et al. Durability of response following cessation of tadalafil taken once daily as treatment for erectile dysfunction. *J Sex Med* 2010; **7**: 3487–94.

75 Gur S, Sikka SC, Hellstrom WJ. Novel phosphodiesterase-5 (PDE5) inhibitors in the alleviation of erectile dysfunction due to diabetes and ageing-induced oxidative stress. *Expert Opin Investig Drugs* 2008; **17**: 855–64.

76 Prince WTCA, Tong W et al. SLx-2101, a new long-acting PDE5 inhibitor: preliminary safety, tolerability, PK and endothelial function effects in healthy subjects. *J Sex Med* 2006; **3**(Suppl.): 29–30.

77 Sweetnam PCS, Grogan M et al. SLx-2101, a novel long-acting phosphodiesterase-5 (PDE5) inhibitor for erectile dysfunction: in vivo and in vitro studies [abstract no. 51]. *J Sex Med* 2006; **3**(Suppl.): 29–30.

78 Heinig R, Weimann B, Dietrich H, Bottcher MF. Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. 2010 (null) ed. *Clin Drug Investig* 2011; **31**(1): 27–41.

79 Boolell M, Gepi-Attee S, Gingell JC, Allen MJ. Sildenafil, a novel effective oral therapy for male erectile dysfunction. *Br J Urol* 1996; **78**(2): 257–61.

80 Doggrell SA. Comparison of clinical trials with sildenafil, vardenafil and tadalafil in erectile dysfunction. *Expert Opin Pharmacother* 2005; **6**(1): 75–84.

81 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers ED, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* 1998; **338**(20): 1397–404.

82 Müller MJ, Ruof J, Graf-Morgenstern M, Porst H, Benkert O. Quality of partnership in patients with erectile dysfunction after sildenafil treatment. *Pharmacopsychiatry* © Georg Thieme Verlag Stuttgart. New York 2001; **34**(03): 91–5.

83 Choi HK, Ahn TY, Kim JJ et al. A double-blind, randomised- placebo, controlled, parallel group, multicentre, flexible-dose escalation study to assess the efficacy and safety of sildenafil administered as required to male outpatients with erectile dysfunction in Korea. *Int J Impot Res* 2003; **15**(2): 80–6.

84 Meuleman E, Cuzin B, Opsomer RJ et al. A dose-escalation study to assess the efficacy and safety of sildenafil citrate in men with erectile dysfunction. *BJU Int* 2001; **87**(1): 75–81.

85 Tan HM, Moh CL, Mendoza JB et al. Asian sildenafil efficacy and safety study (ASSESS-1): a double-blind, placebo-controlled, flexible-dose study of oral sildenafil in Malaysian, Singaporean, and Filipino men with erectile dysfunction. The Assess-1 Study Group. *Urology* 2000; **56**(4): 635–40.

86 Morales A, Gingell C, Collins M, Wicker PA, Osterloh IH. Clinical safety of oral sildenafil citrate (VIAGRA) in the treatment of erectile dysfunction. *Int J Impot Res* 1998; **10**(2): 69–73; discussion 73–4.

87 Stark S, Sachse R, Liedl T et al. Vardenafil increases penile rigidity and tumescence in men with erectile dysfunction after a single oral dose. *Eur Urol* 2001; **40**(2): 181–8; discussion 189–90.

88 Porst H, Rosen R, Padma-Nathan H et al. The efficacy and tolerability of vardenafil, a new, oral, selective phosphodiesterase type 5 inhibitor, in patients with erectile dysfunction: the first at-home clinical trial. *Int J Impot Res* 2001; **13**(4): 192–9.

89 Hellstrom WJG, Gittelman M, Karlin G et al. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. *J Androl* 2002; **23**: 763–71.

90 Hellstrom WJG, Gittelman M, Karlin G et al. Sustained efficacy and tolerability of vardenafil, a highly potent selective phosphodiesterase type 5 inhibitor, in men with erectile dysfunction: results of a randomized, double-blind, 26-week placebo-controlled pivotal trial. *Urology* 2003; **61**(4 Suppl. 1): 8–14.

91 Stief C, Porst H, Sáenz De Tejada I, Ulbrich E, Beneke M, Vardenafil Study Group. Sustained efficacy and tolerability with vardenafil over 2 years of treatment in men with erectile dysfunction. *Int J Clin Pract* 2004; **58**(3): 230–9.

92 Sanford M. Vardenafil orodispersible tablet. *Drugs* 2012; **72**: 87–98.

93 Gittelman M, McMahon CG, Rodríguez-Rivera, Beneke M, Ulbrich E, Ewald S. The POTENT II randomised trial: efficacy and safety of an orodispersible vardenafil formulation for the treatment of erectile dysfunction. *Int J Clin Pract* 2010; **64**(5): 594–603.

94 Debruyne FMJ, Gittelman M, Sperling H, Borner M, Beneke M. Time to onset of action of vardenafil: a retrospective analysis of the pivotal trials for the orodispersible and film-coated tablet formulations. *J Sex Med* 2011; **8**(10): 2912–23.

95 Montorsi F, Verheyden B, Meuleman E et al. Long-term safety and tolerability of tadalafil in the treatment of erectile dysfunction. *Eur Urol* 2004; **45**(3): 339–44; discussion 344–5.

96 Seftel AD, Wilson SK, Knapp PM, Shin J, Wang WC, Ahuja S. The efficacy and safety of tadalafil in United States and Puerto Rican men with erectile dysfunction. *J Urol* 2004; **172**(2): 652–7.

97 Brock GB, McMahon CG, Chen KK et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. *J Urol* 2002; **168**(4 Pt 1): 1332–6.

98 Seftel AD. Challenges in oral therapy for erectile dysfunction. *J Androl* 2002; **23**: 729–36.

99 Cheitlin MD, Hutter AM, Brindis RG et al. Use of sildenafil (Viagra) in patients with cardiovascular disease. Technology and Practice Executive Committee. *Circulation* 1999; **99**(1): 168–77.

100 Goldstein I, McCullough AR, Jones LA et al. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med* 2012; **9**: 1122–33.

101 Hellstrom JG, Freier MT, Serefoglu EC Onset of action and time to efficacy of avanafil, a novel, rapid-onset PDE5 inhibitor in men with mild to severe erectile dysfunction: data from phase 2 and phase 3 clinical trails. *Presented at the American Urological Association (AUA) Annual Meeting* 2012:Poster # MP-53.

102 Fusco F, Razzoli E, Imbimbo C et al. A new era in the treatment of erectile dysfunction: chronic phosphodiesterase type 5 inhibition. *BJU Int* 2010; **105**: 1634–9.

103 Martin-Morales A, Haro JM, Beardsworth A et al. Therapeutic effectiveness and patient satisfaction after 6 months of treatment with tadalafil, sildenafil, and vardenafil: results from the erectile dysfunction observational study (EDOS). *Eur Urol* 2007; **51**: 541–50; discussion 50.

104 Jiann BP, Yu CC, Su CC, Tsai JY. Compliance of sildenafil treatment for erectile dysfunction and factors affecting it. *Int J Impot Res* 2006; **18**: 146–9.

105 Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? *Drugs* 2005; **65**(12): 1621–50.

106 Jarow JP, Burnett AL, Geringer AM. Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment. *J Urol* 1999; **162**(3 Pt 1): 722–5.

107 McMahon CN, Smith CJ, Shabsigh R. Treating erectile dysfunction when PDE5 inhibitors fail. *BMJ* 2006; **332**: 589–92.

108 Son H, Park K, Kim SW, Paick J-S. Reasons for discontinuation of sildenafil citrate after successful restoration of erectile function. *Asian J Androl* 2004; **6**: 117–20.

109 Hanson-Divers C, Jackson SE, Lue TF et al. Health outcomes variables important to patients in the treatment of erectile dysfunction. *J Urol* 1998; **159**: 1541–7.

110 Lee J, Pommerville P, Brock G et al. Physician-rated patient preference and patient- and partner-rated preference for tadalafil or sildenafil citrate: results from the Canadian 'Treatment of Erectile Dysfunction' observational study. *BJU Int* 2006; **98**(3): 623–9.

111 Govier F, Potempa A-J, Kaufman J et al. A multicenter, randomized, double-blind, crossover study of patient preference for tadalafil 20 mg or sildenafil citrate 50 mg during initiation of treatment for erectile dysfunction. *Clin Ther* 2003; **25**: 2709–23.

112 von Keitz A, Rajfer J, Segal S et al. A multicenter, randomized, double-blind, crossover study to evaluate patient preference between tadalafil and sildenafil. *Eur Urol* 2004; **45**: 499–507; discussion 9.

113 Ströberg P, Hedelin H, Ljunggren C. Prescribing all phosphodiesterase 5 inhibitors to a patient with erectile dysfunction – a realistic and feasible option in everyday clinical practice – outcomes of a simple treatment regime. *Eur Urol* 2006; **49**(5): 900–7; discussion 907.

114 Porst H, Kleingarn M, Arnds S. The two PDE 5 inhibitors sildenafil and tadalafil-results of an independent intraindividual comparative trial. *Eur Urol Suppl* 2004; **3**(2): 27.

115 Porst H, Arnds S, Kleingarn M. The three PDE 5 inhibitors sildenafil, tadalafil, and vardenafil-results of a comparative preference trial in 222 patients with erectile dysfunction. *Eur Urol* 2004; **2**(Suppl.

3): 408.Available at: http://scholar.google.com/scholar?q=related:lfjDu1-N1xQJ:scholar.google.com/&hl=en&num=30&as_sdt=0,5&as_ylo=2004&as_yhi=200

116 Claes H, Van Poppel H. The use of sildenafil, tadalafil, and vardenafil in clinical practice. *J Sex Med* 2005; **2**(Suppl. 1): 21. Available at: http://scholar.google.com/scholar?q=related:36lyHRBjqXYJ:scholar.google.com/&hl=en&num=30&as_sdt=0,5.

117 Mirone V, Fusco F, Rossi A et al. Tadalafil and vardenafil vs sildenafil: a review of patient-preference studies. *BJU Int* 2009; **103**: 1212–7.

118 Mulhall JP. Understanding erectile dysfunction medication preference studies. *Curr Opin Urol* 2004; **14**(6): 367–73.

119 Hatzimouratidis K, Amar E, Eardley I et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. 2010(null) ed. *Eur Urol* 2010; 804–14.

120 Donatucci CF, Wong DG, Giuliano F et al. Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. *Curr Med Res Opin* 2008; **24**: 3383–92.

121 Rajfer J, Aliotta PJ, Steidle CP et al. Tadalafil dosed once a day in men with erectile dysfunction: a randomized, double-blind, placebo-controlled study in the US. *Int J Impot Res* 2007; **19**: 95–103.

122 Bella AJ, DeYoung LX, al-Numi M, Brock GB. Daily administration of phosphodiesterase type 5 inhibitors for urological and nonurological indications. *Eur Urol* 2007; **52**: 990–1005.

123 Wrishko R, Sorsaburu S, Wong D et al. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. *J Sex Med* 2009; **6**: 2039–48.

124 Montorsi F, Aversa A, Moncada I et al. A randomized, double-blind, placebo-controlled, parallel study to assess the efficacy and safety of once-a-day tadalafil in men with erectile dysfunction who are naive to PDE5 inhibitors. *J Sex Med* 2011; **8**: 2617–24.

125 Shabsigh R, Donatucci C, Costabile R et al. Reliability of efficacy in men with erectile dysfunction treated with tadalafil once daily after initial success. *Int J Impot Res* 2010; **22**: 1–8.

126 Caretta N, Palego P, Ferlin A et al. Resumption of spontaneous erections in selected patients affected by erectile dysfunction and various degrees of carotid wall alteration: role of tadalafil. *Eur Urol* 2005; **48**: 326–31; discussion 31–2.

127 Behr-Roussel D, Gorny D, Mevel K et al. Chronic sildenafil improves erectile function and endothelium-dependent cavernosal relaxations in rats: lack of tachyphylaxis. *Eur Urol* 2005; **47**(1): 87–91.

128 Desouza C, Parulkar A, Lumpkin D, Akers D, Fonseca V. Acute and chronic effects of low dose sildenafil on endothelial function in type 2 diabetes. *Diabetes* 2001; **50**(Suppl. 2): A110. Available at: http://scholar.google.com/scholar?q=related:iAYok_nJjJIJ:scholar.google.com/&hl=en&num=30&as_sdt=0,5

129 Foresta C, Ferlin A, De Toni L et al. Circulating endothelial progenitor cells and endothelial function after chronic Tadalafil treatment in subjects with erectile dysfunction. *Int J Impot Res* 2006; **18**(5): 484–8.

130 Porst H. [Therapy of erectile dysfunction in 2005]. *Urologe A* 2003; **42**(10): 1330–6.

131 Amr Abdel Raheem PK. Patient preference and satisfaction in erectile dysfunction therapy: a comparison of the three phosphodiesterase-5 inhibitors sildenafil, vardenafil and tadalafil. *Patient Prefer Adherence* Dove Press 2009; **3**: 99.

132 Rubio-Aurioles E, Porst H, Kim ED et al. A randomized open-label trial with a crossover comparison of sexual self-confidence and other treatment outcomes following tadalafil once a day vs. tadalafil or sildenafil on-demand in men with erectile dysfunction. *J Sex Med* 2012; **9**: 1418–29.

133 Perimenis P, Roumeguere T, Heidler H, Roos E, Belger M, Schmitt H. Evaluation of patient expectations and treatment satisfaction after 1-year tadalafil therapy for erectile dysfunction: the DETECT study. *J Sex Med* 2009; **6**(1): 257–67.

134 Ljunggren C, Hedelin H, Salomonsson K, Ströberg P. Giving patients with erectile dysfunction the opportunity to try all three available phosphodiesterase type 5 inhibitors contributes to better long-term treatment compliance. *J Sex Med* 2008; **5**(2): 469–75.

135 Kell PD, Hvidsten K, Morant SV, Harnett JP, Bridge S. Factors that predict changing the type of phosphodiesterase type 5 inhibitor medication among men in the UK. *BJU Int* 2007; **99**(4): 860–3.

136 Mulhall JP, McLaughlin TP, Harnett JP, Scott B, Burhani S, Russell D. Medication utilization behavior in patients receiving phosphodiesterase type 5 inhibitors for erectile dysfunction. *J Sex Med* 2005; **2**(6): 848–55.

137 Althof SE. When an erection alone is not enough: biopsychosocial obstacles to lovemaking. *Int J Impot Res* 2002; **14**(Suppl. 1): S99–104.

138 Jensen PK, Burnett JK. Erectile dysfunction. Primary care treatment is appropriate and essential. *Adv Nurse Pract* 2002; **10**: 45–7.

139 Topol E. *The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care*, 1st edn. New York, NY: Basic Books, 2012.

140 Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging to help patients with HIV infection. *Cochrane Database Syst Rev* 2012; **3**: CD009756.

141 Márquez-Contreras E, Martell-Claros N, Gil-Guillén V et al. Efficacy of a home blood pressure monitoring programme on therapeutic compliance in hypertension: the EAPACUM-HTA study. *J Hypertens* 2006; **24**: 169–75.

142 Munger MA, Stoddard GJ, Wenner AR et al. Safety of prescribing PDE-5 inhibitors via e-medicine vs traditional medicine. *Mayo Clin Proc* 2008; **83**(8): 890–6.

143 Jones MJ. Internet-based prescription of sildenafil: a 2104-patient series. *J Med Internet Res* 2001; **3**(1): E2.

144 Leusink PM, Aarts E. Treating erectile dysfunction through electronic consultation: a pilot study. *J Sex Marital Ther* 2006; **32**(5): 401–7.