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PERSPECTIVE

Sildenafil/Viagra in the treatment of premature ejaculation

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Abstract
The arrival of Pfizer's blue pill Sildenafil in 1998 brought a great relief both to patient and physician signalling the start of a great era of medical therapy in sexual medicine. Since then the sexual medicine experts have been prescribing sildenafil in erectile dysfunction with acceptable minor adverse events. But the use of sildenafil in premature ejaculation (PE) is still debated. 2018 being the 20th anniversary of sildenafil, we have compiled interesting facts about the role of sildenafil in PE from various original articles, systematic reviews, meta-analyses, economic brochures and sexual medicine committee guidelines. The major issues in most of these studies were the heterogeneity in the definition of PE and estimating the exact ejaculatory latency time. This perspective article highlights the positive role of sildenafil in the management of PE (even without ED) with acceptable adverse events. Now that we have a standardised definition of PE from International Society of Sexual Medicine (ISSM) and a psychogenic component in PE definition, more randomised placebo-controlled studies are required to further establish its role.

Discovery and evolution of Sildenafil (Viagra®)

Sildenafil (Viagra®; Pfizer, New York, USA) was Pfizer's blockbuster wonder drug as "blue pill" for erectile dysfunction (ED) which sold like hot cakes soon after its release. Although it was initially being tested in cardiac trials as a phosphodiesterase type 5 inhibitor (PDE5-I), the discovery that sildenafil could lead to a penile erection was a serendipity, which was noticed by the nurses when they saw men with embarrassment lying on their abdomen to hide their penile erections.

Viagra® was first launched in April 1998 in the United States of America (USA), soon after the Food and Drug Administration (FDA) granted approval, and is now widely available all over the globe [1]. More than $400 million worth of Viagra® was sold in its first quarter on the USA market. By May 8, 1998 (1 month after the launch), more than 300,000 total prescriptions were written for Viagra [2].

"*Hard Sell—The Evolution of A Viagra Salesman*", a book by Jamie Reidy published in 2005 gave an insider look at the pharmaceutical industry from a former salesman of Viagra, discusses how the drug was marketed and the tactics used to persuade the doctors he visited to prescribe the drug. "*Love & Other Drugs*" is a 2010 American erotic romantic comedy—drama film based on this book.

Pfizer's Viagra has continued to earn worldwide revenue of more than 1 billion US dollars every year [3]. Pfizer's patents on Viagra expired outside the USA in 2012; in the USA they are set to expire in 2020. The FDA has approved 15 drug manufacturers to market generic sildenafil in the USA as of 2018, and 7 of these companies are based in India. This is likely to lead to dramatic price reductions [4].

The Debate

20 years since its inception in 1998, we all know the established results of sildenafil in the management of ED, but is there a role for sildenafil in premature ejaculation (PE)? What is the current evidence that we have?

Before that, we need to know the updated definition of PE as there is so much variability in the definition across different societies.

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Definition of PE

International Society of Sexual Medicine (ISSM) convened a second Ad Hoc Committee for the Definition of PE in Bangalore, India in April 2013 and came up with the first evidence based definition for PE [5].

PE (lifelong and acquired) is a male sexual dysfunction characterised by the following:

- Ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 min or less (acquired PE).
- The inability to delay ejaculation on all or nearly all vaginal penetrations.
- Negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy.

Rationale for using Sildenafil in PE

There are three stages in ejaculation: emission, ejection and orgasm. Emission involves contraction of seminal vesicles (SV) and prostate, with expulsion of semen into the posterior urethra and is mediated by sympathetic nerves (T10–L2). Ejection is mediated by somatic nerves (S2–4) and involves pulsatile contractions of the bulbocavernosus and pelvic floor muscles along with relaxation of the external urinary sphincter [6].

Central nervous system (CNS): Medial preoptic area (MPOA) is involved in ejaculation [7]. The neurotransmitters such as serotonin and nitric oxide (NO) are involved in ejaculation [8]. NO has a central effect, mostly in the MPOA, in promoting penile erection, and it may inhibit seminal emission. PDE5 has been expressed in the CNS, and PDE5-Is can cross the blood–brain barrier into the brain. Experimental administration of sildenafil intrathecally in rats increases NO and cGMP in the MPOA [9]. A decrease of sympathetic tone by increased NO activity in the MPOA is related to inhibition of ejaculation.

Peripheral NS: Similar to NO-cGMP and NO-cyclic adenosine monophosphate (cAMP) signalling pathways that are involved in relaxation of corporal smooth muscles in corpus cavernosum, they might also relax the smooth muscles in VD, SVs, prostate and urethra causing delay in emission [10].

There are several mechanisms [11, 12] to explain the effectiveness of sildenafil (PDE5-Is) for treatment of PE:

- Centrally, through the nitric oxide/cyclic guanosine monophosphate pathway.
- Peripherally by causing relaxation of smooth muscle in the vas deferens, SV, prostate, and urethra and inhibition of adrenergic transmission.
- Locally by inducing peripheral analgesia.
- Prolongation of the duration of erection.

Ückert et al. [13] examined the effects of selective PDE-I on both spontaneous and electrically induced phasic contractions of isolated human SV smooth muscle. Mean maximum inhibition of SV contraction to electrical stimulus was determined as −89.6% with rolipram (PDE4-I), −61.3% with sildenafil (PDE5-I), −62% with vardenafil (PDE5-I) and −46% with vinpocetine (PDE1-I). The frequency of the spontaneous contractions was reduced by 50% in the presence of 2 μM rolipram, 5 μM sildenafil or vardenafil, and 8 μM vinpocetine. This study provided more impetus for further research to establish the role of PDE5-I in PE.

Various other studies [14, 15] have confirmed the inhibition of SV contraction by sildenafil in human and animal models.

McMahon et al. [16] stressed upon reduced performance anxiety because of better erections and down-regulation of the erectile threshold to a lower level of arousal so that increased levels of arousal are required to achieve the ejaculation threshold have also been suggested as potential mechanisms.

Current evidence on the role of Sildenafil in PE

ISSM, in its quick reference guide to PE (version 2015) [17], does not mention sildenafil in the list of recommended pharmacological treatments for PE. Dapoxetine is the only selective serotonin receptor inhibitor (SSRI) approved for on-demand treatment of PE in European countries and elsewhere, but not in the USA [18]. Other drugs such as paroxetine (SSRI), sertraline (SSRI), clomipramine and tramadol continue to be used as off-label medications in PE [19]. The numerous precautions and adverse events associated with long-term SSRIs have made many to re-consider the use of PDE5-I in PE [20].

The American Urological Association (AUA) clinical guidelines on PE which was first published in 2004 and last reviewed in 2010, does not list PDE5-I in its table showing medical therapy options for the treatment of PE [21].

Based on several open label studies, the latest European Association of Urology (EAU) 2018 guidelines [18] has a "strong" recommendation for the use of sildenafil (PDE5-I) alone or in combination with other therapies in patients with PE (without ED).

The controversial role of PDE5-I in the treatment of PE was debated in 2011 by Jannini et al. [22] with four other experts in this field. The report concluded that PDE5-Is are

the first choice in patients with comorbid ED and PE (where one may be secondary to the other), well-designed studies on the possible use of PDE5-Is in PE patients without ED are still limited.

A well-designed, randomised, double-blind, placebo-controlled study by McMahon et al. [16] in 2005 compared sildenafil to placebo in PE. Among the 144 patients (placebo = 71, sildenafil = 73) aged 18–65 years, the change in intravaginal ejaculatory latency time (IELT) and vibrotactile stimulation ELT were higher in sildenafil group, but did not reach statistical significance. However, patients who took sildenafil reported significantly increased ejaculatory control (1.8 ± 0.3 vs. 1.5 ± 0.3), increased ejaculatory confidence (2.2 ± 0.2 vs. 1.9 ± 0.2), and improved overall sexual satisfaction scores (3.1 ± 0.2 vs. 2.8 ± 02) on the index of PE questionnaire, and had a decreased post-ejaculatory erectile refractory time (3.2 ± 0.7 vs. 6.4 ± 0.7 min).

Multicentric study [23] by Wang and Ralph in 2007 showed that sildenafil 50 mg was very effective and had much higher efficacy than paroxetine 20 mg and squeeze technique in 108 patients. At 3 and 6 months, there was significant improvement in IELT and intercourse satisfactory score (ISS) with sildenafil.

A single-centre, single-blind, placebo-controlled clinical trial by Gameel et al. [24] conducted on 150 patients who had PE for >1 year showed that all four on-demand drugs (tramadol 50 mg, sildenafil 50 mg, paroxetine 20 mg and topical lidocaine gel 2.5%) improved IELT values over placebo. Tramadol was associated with significantly longer IELT values, whilst sildenafil-induced significantly better sexual satisfaction than the other drugs.

The effects of three individual PDE5-Is (placebo, vardenafil 10 mg, sildenafil 50 mg or tadalafil 20 mg) in PE were assessed by Gökçe et al. [25] in a double-blind study design in 80 patients (20 in each group). The study concluded that median duration of vibratory stimulation (ELT) of subjects was 48.5 s in placebo groups, 53.5 s for sildenafil, 70 s for tadalafil and 82.5 s for vardenafil. Compared with the placebo group, ELT was significantly longer only in subjects receiving vardenafil.

In the 2013 Global Online Sexuality Survey (GOSS) on PDE5-I utilisation among English speakers in USA [26] revealed that recreational users diagnosed with PE (as evaluated by the Premature Ejaculation Diagnostic Tool [PEDT]) reported the effect of PDE5-Is as "excellent" in 30.5%, "very good" in 36.1%, "good" in 25%, "weak" in 5.6% and "none" in 2.8%. Sildenafil was the most commonly used PDE5-I when either bought through a prescription receipt or ordered online.

There has been a recent shift in the treatment paradigm to combined therapy in PE. Two meta-analyses [27, 28] showed that combined therapy (PDE5-I and SSRI) was better than PDE5-I alone, SSRI alone or placebo in PE. But an another meta-analysis [29] showed that the combined treatment of PDE5-I and SSRI although more efficacious, had more side effects. PDE5-I was significantly more effective than a placebo or SSRI for treating PE. A randomised placebo-controlled trial on 150 patients by Abu El-Hamd et al. [30] concluded that the combined dapoxetine with sildenafil therapy could significantly improve PE patients without ED as compared to paroxetine alone or dapoxetine alone or sildenafil alone with tolerated adverse effects.

A recent 2017 systematic review and meta-analysis of 15 RCTs by Martyn-St. James et al. [31] on PDE5-I for PE concluded that PDE5-Is are significantly more effective than placebo, and PDE5-Is combined with an SSRI are significantly more effective than SSRIs alone at increasing IELT and improving other effectiveness outcomes. There was heterogeneity across RCTs, as the methodological quality of majority of RCTs in this meta-analysis was unclear.

There is significant heterogeneity in most of the study design in PE and the same has been highlighted in Table 1.

Safety profile of Sildenafil

A systematic review and meta-analysis by Tsertsvadze et al. [32] in 2009 on harms of sildenafil revealed that the rates of serious adverse events and withdrawals because of adverse events did not differ in sildenafil vs. placebo groups.

A multicentric study on long-term (4-year study period) safety and effectiveness of sildenafil in men with ED by McMurray et al. [33] involving 979 participants noted that 37 (3.8%) of the men had 1 or more adverse events that led to changes in dosing or temporary or permanent discontinuation. Of the 47 events, headache and dyspepsia were most common ($n = 10$ each), followed by rhinitis ($n = 6$), flushing ($n = 5$), abnormal vision ($n = 4$), dizziness ($n = 3$) and 1 report each of mild palpitations, moderate tachycardia, diarrhoea, nausea, myalgia, hypertonia, respiratory disorder, conjunctivitis and photophobia.

Sildenafil has a tenfold lower affinity for PDE6 compared with PDE5 [34]. The potential effects of sildenafil-induced vasodilation on the ocular circulation and sildenafil inhibition of PDE6 on the visual function have been intensively studied during preclinical development and in clinical trials conducted before and after sildenafil was approved for marketing. Various reports [35, 36] on visual function studies suggest that sildenafil does not affect visual acuity, visual fields, and contrast sensitivity. Minor, transient visual symptoms, reported as blue tinge to vision, increased brightness of lights, and blurry vision, have been reported with sildenafil use and occur more frequently at higher doses, particularly at the time of peak plasma levels [37].

Table 1 Methodology and conclusions of different publications involving sildenafil in PE

Study	PE criteria	Treatment	Endpoints	Conclusion
Tang et al. [43]	Not reported	Sildenafil 50 mg + BT, BT alone, sertraline + BT	IELT, patient-partner sexual satisfaction Likert scale 0–5	If PE + ED, sildenafil may be used
McMahon et al. [16]	DSM-IV, IELT 2 min,	Sildenafil 50–100 mg, placebo	IELT, vibrotactile stimulation ELT, IPE, AEs	Sildenafil increased confidence, the perception of ejaculatory control, and overall sexual satisfaction
Wang et al. [23]	IELT 2 min	Sildenafil 50 mg, paroxetine 20 mg, squeeze technique	IELT, PE grade, ISS, frequency of intercourse, AEs	Effective and safe. More effective than paroxetine and squeeze technique
Gökçe et al. [25]	IELT < 1 min in > 50% intercourse attempts	Sildenafil 50 mg, vardenafil 10 mg, tadalafil 20 mg, placebo	Visual-vibrator induced ELT	PDE5-Is seem to prolong ELT
Gameel et al. [24]	IELT of < 2 min in > 75% of episodes	Sildenafil 50 mg + LG, tramadol 50 mg + LG, paroxetine 20 mg + LG, topical 2.5% lidocaine gel + oral multivitamin, placebo (oral multivitamin + LG)	IELT, sexual satisfaction scale 0–5, AEs	Sildenafil improved IELT. Sildenafil induced significantly better sexual satisfaction
Abu El-Hamd and Abdelhamed [30]	ISSM 2014 definition [5]	30 mg dapoxetine + 50 mg sildenafil, placebo (multivitamin), 30 mg paroxetine, 30 mg dapoxetine, 50 mg sildenafil	PEDT, stopwatch IELT, sexual satisfaction treatment scale of 0–5 as proposed by Kim and Paick [44]	Combined therapy (Dapo + Sil) had better outcomes compared to other monotherapy arms in all three endpoints

BT behavioural therapy, *IELTS* intravaginal ejaculatory latency time, *DSM-IV* Diagnostic and Statistical Manual IV criteria, *IPE* index of premature ejaculation questionnaire, *ISS* intercourse satisfactory score, *AE* adverse events, *LG* lubricating gel, *PEDT* premature ejaculation diagnostic tool

Dose modifications

Sildenafil is metabolised primarily by the cytochrome P450 enzyme 3A4, hence one must take into account the interaction between sildenafil and other drugs that are also metabolized by 3A4, because enzymes that compete with sildenafil for 3A4, especially those that are inhibitors of the enzyme, could cause unwanted pharmacological effects such as elevated and prolonged serum concentrations of sildenafil [38].

Hence, start with lower doses of sildenafil in patients who are on drugs that inhibit the CYP34A pathway (indinavir, atazanavir, ketoconazole, ritonavir, clarithromycin and itraconazole). Start with higher doses of sildenafil in patients who are on drugs which induce CYP3A4 and enhance the breakdown of PDE5-Is (rifampin, phenobarbital, phenytoin and carbamazepine) [18].

Food for thought

The patient perceived PE could sometimes be an exaggerated complaint or unrealistic expectation of ejaculatory time. In the Middle East, in the Global Online Sexuality Survey (GOSS) [39], PE had an overwhelming prevalence of 82.6%, despite an acceptable median IELT of 5 min.

A similar online survey of 610 men in the USA [40] about PE revealed that 25%, 21% and 51% reported an IELT of >10, 5–10 and < 5 min, and surprisingly 77% expected more than 5 min of IELTs for a normal person.

There is a significant psychogenic component associated with PE. Jannini et al. [22] pointed out that in some patients, PE can be a conscious or unconscious "bed trick" to admit to less humiliating PE caused by "enthusiasm", than to ED. Some even ejaculate early to hide the reduced rigidity of the erection. So the possibility that other sexual dysfunction issues co-exist with PE should always be thoroughly evaluated.

Considering the psychogenic component in the definition of PE, there is significant need to evaluate placebo effect in all studies pertaining to management of PE. Hence it is wiser to design placebo-controlled studies when assessing the effect of PDE5-Is on PE.

The only well-designed randomised study supporting the role of PDE5-I in PE was by McMahon et al. [16] in 2005, but the author himself in his systematic review [41] of 14 published studies in 2006 opined against the use of PDE5-I in PE alone.

Special considerations for observational studies and clinical trials in PE has been highlighted in the recent 2017 article [42] "Standards for clinical trials in male and female sexual dysfunction: III. Unique aspects of clinical trials in male sexual dysfunction". It is time we embrace the strict

uniform criteria across the globe for all clinical trials in PE. The guidelines mention that measured IELT must be considered a standard primary study end-point in PE trials. The stopwatch measurement of IELT is the most accepted as it is considered to be "objective". But practically speaking is it really possible to clock an event accurately with a stopwatch in such an overexcited state while performing sexual intercourse? If stopwatch used, would it not increase the anxiety among couples already anxious about the PE? Future devices which are more convenient involving less attention of the couple during sexual intercourse should be made available. Recently there has been movement away from IELT to just ELT in the interest of eliminating the heterosexual bias.

Conclusion

The evaluation and treatment of PE is complex, and guidelines for such management have recently evolved. Now that we have an evidence based definition for PE from ISSM and standards in sexual dysfunction clinical trials, it's time we start reporting randomised controlled trials using the CONSORT statement. More convenient methods of reporting IELT should be devised to avoid reporting bias. EAU 2018 guidelines has a "strong" recommendation for the use of sildenafil (PDE5-I) alone or in combination with other therapies in patients with PE (without ED), although AUA and ISSM still do not recommend PDE5-I alone in PE (without ED).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. 20895ltr.pdf [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/20895ltr.pdf [cited 2018 Oct 27]
2. Keith A. The economics of Viagra. Health Aff Proj Hope. 2000;19:147–57.
3. A History of Viagra. Available from: https://www.bloomberg.com/news/features/2017-12-11/the-little-blue-pill-an-oral-history-of-viagra; 2017 Dec 11 [cited 2018 Oct 27]
4. Pfizer to lose patent of drug Viagra, Indian companies gear up with copycat versions [Internet]. https://www.hindustantimes.com/. 2018. Available from: https://www.hindustantimes.com/business-news/pfizer-to-lose-patent-of-drug-viagra-indian-companies-gear-up-with-copycat-versions/story-jrBkWfXF1A6fO7insmqmCN.html [cited 2018 Sep 21]
5. Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. J Sex Med. 2014;11:1423–41.
6. Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. J Sex Med. 2010;7(4 Pt 2):1668–86.
7. Hull EM, Du J, Lorrain DS, Matuszewich L. Extracellular dopamine in the medial preoptic area: implications for sexual motivation and hormonal control of copulation. J Neurosci. 1995;15:7465–71.
8. Donatucci CF. Etiology of ejaculation and pathophysiology of premature ejaculation. J Sex Med. 2006;3(Suppl. 4):S303–S8.
9. Sato Y, Zhao W, Christ GJ. Central modulation of the NO/cGMP pathway affects the MPOA-induced intracavernous pressure response. Am J Physiol Regul Integr Comp Physiol. 2001;281:R269–278.
10. Dixon JS, Jen PY. Development of nerves containing nitric oxide synthase in the human male urogenital organs. Br J Urol. 1995;76:719–25.
11. Chen J, Keren-Paz G, Bar-Yosef Y, Matzkin H. The role of phosphodiesterase type 5 inhibitors in the management of premature ejaculation: a critical analysis of basic science and clinical data. Eur Urol. 2007;52:1331–9.
12. Abdel-Hamid IA, Jannini EA, Andersson K-E. Premature ejaculation: focus on therapeutic targets. Expert Opin Ther Targets. 2009;13:175–93.
13. Uckert S, Bazrafshan S, Sonnenberg JE, Kuczyk MA. Effects of phosphodiesterase inhibitors on the contractile responses of isolated human seminal vesicle tissue to adrenergic stimulation. J Sex Med. 2009;6:408–14.
14. Birowo P, Uckert S, Kedia GT, Sonnenberg JE, Sandner P, Thon WF, et al. Exposure of human seminal vesicle tissue to phosphodiesterase (PDE) inhibitors antagonizes the contraction induced by norepinephrine and increases production of cyclic nucleotides. Urology 2010;76:1518.e1-6.
15. Orhan I, Onur R, Taşdemir C, Ayar A, Kadioğlu A. Sildenafil citrate inhibits agonist induced contractions in isolated rat seminal vesicles. J Urol. 2006;175:2350–3.
16. McMahon CG, Stuckey BGA, Andersen M, Purvis K, Koppiker N, Haughie S, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. J Sex Med. 2005;2:368–75.
17. ISSM-Quick-Reference-Guide-to-PE.pdf [Internet]. Available from: https://professionals.issm.info/wp-content/uploads/sites/2/2018/05/ISSM-Quick-Reference-Guide-to-PE.pdf [cited 2018 Sep 21]
18. Hatzimouratidis K, Eardley I, Giuliano F, Moncada I, Salonia A. Male sexual dysfunction [Internet]. Uroweb. Available from: http://uroweb.org/guideline/male-sexual-dysfunction/ [cited 2018 Sep 21].
19. McMahon CG. Current and emerging treatments for premature ejaculation. Sex Med Rev. 2015;3:183–202.
20. Cartwright C, Gibson K, Read J, Cowan O, Dehar T. Long-term antidepressant use: patient perspectives of benefits and adverse effects. Patient Prefer Adherence. 2016;10:1401–7.
21. Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JPW, Lue TF, et al. AUA guideline on the pharmacologic management of premature ejaculation. J Urol. 2004;172:290–4.
22. Jannini EA, McMahon C, Chen J, Aversa A, Perelman M. The controversial role of phosphodiesterase type 5 inhibitors in the treatment of premature ejaculation. J Sex Med. 2011;8:2135–43.
23. Wang W-F, Wang Y, Minhas S, Ralph DJ. Can sildenafil treat primary premature ejaculation? A prospective clinical study. Int J Urol J Jpn Urol Assoc. 2007;14:331–5.
24. Gameel TA, Tawfik AM, Abou-Farha MO, Bastawisy MG, El-Bendary MA, El-Gamasy AE-N. On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of

premature ejaculation: a randomised placebo-controlled clinical trial. Arab J Urol. 2013;11:392–7.
25. Gökçe A, Halis F, Demirtas A, Ekmekcioglu O. The effects of three phosphodiesterase type 5 inhibitors on ejaculation latency time in lifelong premature ejaculators: a double-blind laboratory setting study. BJU Int. 2011;107:1274–7.
26. Shaeer O. The Global Online Sexuality Survey (GOSS): the United States of America in 2011 chapter II: phosphodiesterase inhibitors utilization among English speakers. J Sex Med. 2013;10:532–40.
27. Men C, Yu L, Yuan H, Cui Y. Efficacy and safety of phosphodiesterase type 5 inhibitors on primary premature ejaculation in men receiving selective serotonin reuptake inhibitors therapy: a systematic review and meta-analysis. Andrologia. 2016;48:978–85.
28. Bai Y, Pu C, Han P, Li J, Yuan H, Tang Y, et al. Selective serotonin reuptake inhibitors plus phosphodiesterase-5 inhibitors for premature ejaculation: a systematic review and meta-analysis. Urology. 2015;86:758–64.
29. Sun Y, Luo D, Yang L, Tang C, Yang T, Hu X, et al. Efficacy of phosphodiesterase-5 inhibitor in men with premature ejaculation: a new systematic review and meta-analysis. Urology. 2015;86:947–54.
30. Abu El-Hamd M, Abdelhamed A. Comparison of the clinical efficacy and safety of the on-demand use of paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil in treatment of patients with premature ejaculation: a randomised placebo-controlled clinical trial. Andrologia. 2018;50.
31. Martyn-St James M, Cooper K, Ren S, Kaltenthaler E, Dickinson K, Cantrell A, et al. Phosphodiesterase Type 5 inhibitors for premature ejaculation: a systematic review and meta-analysis. Eur Urol Focus. 2017;3:119–29.
32. Tsertsvadze A, Yazdi F, Fink HA, MacDonald R, Wilt TJ, Bella AJ, et al. Oral sildenafil citrate (viagra) for erectile dysfunction: a systematic review and meta-analysis of harms. Urology. 2009;74:831–836.e8.
33. McMurray JG, Feldman RA, Auerbach SM, DeRiesthal H, Wilson N. Long-term safety and effectiveness of sildenafil citrate in men with erectile dysfunction. Ther Clin Risk Manag. 2007;3:975–81.
34. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. J Urol. 1998;159:2164–71.
35. Moschos MM, Nitoda E. Pathophysiology of visual disorders induced by phosphodiesterase inhibitors in the treatment of erectile dysfunction. Drug Des Devel Ther. 2016;8:3407–13.
36. Wirostko BM, Tressler C, Hwang L-J, Burgess G, Laties AM. Ocular safety of sildenafil citrate when administered chronically for pulmonary arterial hypertension: results from phase III, randomised, double masked, placebo controlled trial and open label extension. Br Med J. 2012;344:e554.
37. Laties A, Sharlip I. Ocular safety in patients using sildenafil citrate therapy for erectile dysfunction. J Sex Med. 2006;3:12–27.
38. Pentyala S, Rahman A, Mishra S, Muthiki S, Hughes E, Bikkani A, et al. Pharmacokinetic drug interactions of phosphodiesterase-5 inhibitors mediated by cytochrome P450 3A4 isoform. 10.
39. Shaeer O, Shaeer K. The Global Online Sexuality Survey (GOSS): ejaculatory function, penile anatomy, and contraceptive usage among Arabic-speaking Internet users in the Middle East. J Sex Med. 2012;9:425–33.
40. Shaeer O, Shaeer K, Serefoglu EC, Fode M. 381 Premature ejaculation among english-speaking male internet users in the USA: Results From the Global Online Sexuality Survey (GOSS) 2015. J Sex Med. 2017 (1):S112–3.
41. McMahon CG, McMahon CN, Leow LJ, Winestock CG. Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. BJU Int. 2006;98:259–72.
42. Fisher WA, Gruenwald I, Jannini EA, Lev-Sagie A, Lowenstein L, Pyke RE, et al. Standards for Clinical Trials in Male and Female Sexual Dysfunction: III. Unique Aspects of Clinical Trials in Male Sexual Dysfunction. J Sex Med. 2017;14:3–18.
43. Tang W, Ma L, Zhao L, Liu Y. Efficacy and safety of Sertraline, Viagra and Cardura in patients with premature ejaculation [Internet]; 2014. Available from: http://en.cnki.com.cn/Article_en/CJFDTOTAL-NXXX200406007.htm. [cited 2018 Sep 21]
44. Kim SW, Paick JS. Short-term analysis of the effects of as needed use of sertraline at 5 PM for the treatment of premature ejaculation. Urology. 1999;54:544–7.