Efficacy and safety of PDE5 inhibitors in the treatment of diabetes mellitus erectile dysfunction: a systematic review and meta-analysis

Xiao Li
Department of Andrology, The first affilated hospital of henan University of Chinese Medicine
Qi Zhao
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Jingshang Wang
Beijing Obstetrics and Gynecology Hospital
Jisheng Wang
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Hengheng Dai
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Yanfeng Li
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Fei Chen
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Bin Wang
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital
Haisong Li (1028bj@sina.com)
Beijing University of Chinese Medicine Affiliated Dongzhimen Hospital https://orcid.org/0000-0003-0878-0294

Research article

Keywords: PDE5 inhibitors, diabetes mellitus erectile dysfunction, systematic review

Posted Date: August 28th, 2019

DOI: https://doi.org/10.21203/rs.2.10685/v1

Abstract

ABSTRACT Background: To systematically evaluate the efficacy and safety of the PDE5 inhibitors in patients with diabetes mellitus erectile dysfunction (DMED). Methods:Random control trials (RCTs) in PubMed, EMBASE, Cochrane library, ClinicalTrials, China Knowledge Network (CNKI), Weipu Chinese Science and Technology Journal Full-text Database (VIP), Wanfang Data Resource System (WANFANG) were searched. Two researchers independently screened the literature, extracted the data and checked the results, and used the risk assessment tool to conduct a methodological quality assessment, and finally conducted a meta-analysis. The primary outcome, the erectile function scores of the International Index of Erectile Dysfunction (IIEF-EF), was recorded, while secondary outcomes (IIEF-Q3, IIEF-Q4, SEP 2 and 3, GAQ) and safety outcomes also needed attention. Results: Twelve studies included 3,124 patients and six PDE5 inhibitors were included. Compared with placebo, PDE5 inhibitors significantly improved male erectile function in IIEF-EF (WMD = 5.73; 95% CI: 3.62 to 7.84), IIEF-Q3 (WMD = 1.14; 95% CI: 0.87 to 1.40), IIEF-Q4 (WMD=1.28; 95% CI: 1.04 to 1.51), SEP2 (WMD=21.24; 95% CI: 15.50 to 26.98), SEP3 (WMD=25.77; 95% CI: 18.78 to 32.77), GAQ (RR) =2.98; 95% CI: 2.06 to 4.32), and with the safety (WMD=5.73; 95% CI: 3.62 to 7.84). Conclusions: PDE5 inhibitors can significantly improve the patient's erectile function, but cannot ignore their side effects.

Background

Diabetes mellitus erectile dysfunction (DMED) is one of the common chronic complications of diabetes mellitus (DM), [1] which is also an important type of erectile dysfunction (ED), with the main manifestation of not being able to achieve and/or maintain adequate erection to achieve a satisfactory sexual life. [2,3] Compared with healthy men, the probability of ED in diabetic patients is 1.9-4 times that of healthy men. [4] As long-term hyperglycemia can damage the patient's vascular endothelium, nerves and endocrine, finally the erectile function of the corpus cavernosum is also seriously affected.[5,6] According to research, approximately 75% of diabetic men suffered from ED. [7]

However, due to the complex effects of blood vessels and neuropathy, DMED is more difficult to treat than normal ED. [8] Currently, Phosphodiesterase-5 (PDE5) inhibitors are the first line of treatment for ED. Nowadays, more and more PDE5 inhibitors, such as avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil and vardenafil, meets the sexual demanding of DMED patients and their partners. [9] And every coin has two sides, PDE5 inhibitors also have some side effects like dyspepsia and headache. [10]

Studies have confirmed that PDE5 inhibitors can improve the clinical symptoms of DMED patients. Previous literature search showed that there had been two meta-analyses to explore the efficacy and safety of PDE5 inhibitors in the treatment of DMED, but the above meta-analysis had some limitations such as outcomes and relatively old literature. [11,12] This article intends to use the current latest outcome indicators to conduct meta-analysis of relevant randomized controlled trials, systematically evaluate their effectiveness and safety, and provide more accurate evidence-based medical evidence for the clinical application of PDE5 inhibitors in the treatment of DMED.

Methods

Data Sources and Search Strategy

This systematic review and meta-analysis had registered on PROSPERO (No. CRD42018095185), and the whole protocol were published. [13] The protocol obeyed from Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement guidelines.

Two reviewers (XL and QZ) researched independently the electronic databases including Pubmed, EMBASE, The Cochrane Library, the Chinese BioMedical Literature Database, the China National Knowledge Infrastructure (CNKI), the China Science and Technology Journal database (VIP), and the Wanfang database. The full searching strategy had been showed in our protocol.[13] Retrieve dissertations, ongoing experiments, grey literature, conference and unpublished documents were also searched as the same strategy. The last date of the search was 28 February 2019.

Inclusion and exclusion criteria

Two reviewers (JSW and HHD) gave each articles an assessment independently according to the inclusion and exclusion criteria. The inclusion criteria included (1) randomized controlled trials (RCTs) of PDE5 inhibitors (like avanafil, lodenafil, mirodenafil, sildenafil, tadalafil, udenafil, or vardenafil) for the treatment of DMED; (2)the language of the study limited to Chinese and English; (3) male patients aged over 18 years old; (4) meeting the National Institutes of Health (NIH) ED diagnostic criteria: failure to achieve and/or maintain adequate erection to complete a satisfactory life to determine ED duration ≥ 3 months; treatment time ≥ 12 weeks and the American Diabetes Association (ADA) Diabetes Care Guide[1]: glycated hemoglobin (HbA1c) ≥ 6. 5% or fasting blood glucose (FPG) ≥ 7. 0 mmol / L or glucose tolerance test (OGTT) 2 h, blood glucose ≥ 11. 1 mmol / L or patients with typical symptoms of hyperglycemia or hyperglycemia crisis, random blood glucose ≥ 11. 1 mmol / L. The exclusion criteria were as follows: (1) animal studies; (2) non-randomized design; (3) articles that provided inadequate information of outcomes; (4)studies used combined drug therapy or from the same study population.

Outcomes

The erectile function scores of the International Index of Erectile Dysfunction (IIEF-EF) was the primary outcomes we cared about. We also recorded the following indexes: International Index of Erectile Dysfunction Question 3 (IIEF Q3), International Index of Erectile Dysfunction Question 4 (IIEF Q4), Sexual Encounter Profile Question 2 (SEP2), Sexual Encounter Profile Question 3 (SEP3) and Global Assessment Question (GAQ). And the adverse reactions of patients during medication would be taken seriously. See our protocol for more details.

Study selection and data extraction

All the studies were managed by EndNote X7. Two dependent reviewers (FC and YFL) would read the the topics and abstracts of the studies, and decide whether they met the inclusion criteria. Any disagreement

were discussed by another rich-experienced reviewer (HSL). We would extract necessary information from the included studies: trial characteristics (first author, publication year, sample size, duration of therapy, type and dose of drug), participants' baseline (age, country, type of diabetes) and outcomes. If the data in the literature was inadequate, we would try to contact the corresponding authors by email.

Risk of bias assessment

Risk of bias (ROB) assessment tool would be used to evaluate the quality of each literature. There were six biases including sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting and others bias according to the Cochrane handbook. Two trained review authors (JSW and HHD) gave the article a low bias, unclear, or high bias evaluation. If there was a disagreement among reviewers, it would be discussed with another reviewer (BW) to make a decision. ROB assessment were performed with Review Manager statistical software package (Version 5.3.5).

Data synthesis and statistical analysis

Data synthesis were performed by the STATA statistical software package (Version 12.0). Mean difference (MD) and 95% confidence interval (CI) would be recorded for continuous variable outcome. For dichotomous outcomes, we recorded the relative risk (RR) and 95% CI. Statistical heterogeneity was represented by a standard $\chi 2$ test and I^2 test with a significance level of $p<.1$. When $I^2 < 50\%$ and $P \geq .1$, a fixed-effect model will be used and a random-effects model will be use when $I^2 \geq 50\%$ or $P<.1$. If the heterogeneity is high, we will analyze the cause of the heterogeneity and subgroup analysis will be performed.

Subgroup analysis and Sensitivity analysis

We would make subgroup analysis if there was significant heterogeneity in the final outcomes. And sensitivity analysis would preformed to test the robustness of meta-analysis results.

Results

Search results and study characteristics

According to the search strategy, we retrieved 341 articles from the electronic database and 8 articles from other resources. Among them, 19 articles were repeated, 296 articles were removed according to the bibliography and abstracts, and 34 papers were obtained. Finally, 12 articles [14-25] were selected according to the document exclusion criteria. The literature screening process is shown in Figure 1.

12 placebo randomized controlled trials were included in the study, involving 3,142 patients. The period of each trial was more than 12 weeks, which was performed in different countries, like US, UK, Germany,

Korea and so on. The types of PDE5i included 4 studies of sildenafil [14,15,18,19], 3 Vardenafil [17,20,25], 2 tadalafil [16,21], 1 mirodenafil [22], 1 udenafil [23], and1 avanafil [25]. A total of 4 studies [17,21,23,24] used two doses of PDE5 inhibitor as experimental groups. To avoid bias in meta-analysis, we only extracted data from higher dose groups. Other research characteristics were shown in Table 1.

We assessed risk of bias by the Cochrane Collaboration's tool. The systematic review included studies of RCT studies and blinded approach to participants and personnel (performance bias) and outcome accessment (detection bias). Three studies reported allocation concealment. [18,24,25] In the included literature, relevant outcome measures were reported in the method, so there was no selective bias. The risk of bias assessment of the studies is depicted in Figure 2.

IIEF-EF

A total of 8 articles [14,15-17,20,22,24,25] were included in the literature comparing PDE5 inhibitors with placebo to improve IIEF-EF in patients with DMED. Meta-analysis showed that PDE5 inhibitors were better than placebo in improving IIEF-EF in patients with DMED (WMD=5.73; 95% CI: 3.62 to 7.84; Figure 3) with significant heterogeneity ($P<0.001$; $I^2=77.8\%$), a random effect model was used.

Sexual satisfaction

IIEF-Q3 evaluated ability to achieve erections. A total of 5 articles [14-16,19,22] were included in the literature comparing PDE5 inhibitors with placebo to improve IIEF-Q3 in patients with DMED. Meta-analysis showed that PDE5 inhibitors were better than placebo in improving IIEF-Q3 in patients with DMED (WMD=1.14; 95% CI: 0.87 to 1.40; Figure 4, A) with low heterogeneity ($P=0.198$; $I^2=33.5\%$), a fix effect model was used.

IIEF-Q4 represented ability to maintain erections. A total of 5 articles [14-16,19,22] were included in the literature comparing PDE5 inhibitors with placebo to improve IIEF-Q4 in patients with DMED. Meta-analysis showed that PDE5 inhibitors were better than placebo in improving IIEF-Q4 in patients with DMED (WMD=1.28; 95% CI: 1.04 to 1.51; Figure 4, B), with no heterogeneity ($P=0.523$; $I^2=0\%$), a fixed effect model was used.

SEP2 means whether you are able to insert your penis into your partner's vagina. A total of 3 articles [20,22,23] were included in the literature comparing PDE5 inhibitors with placebo to improve SEP2 in patients with DMED. Meta-analysis showed that PDE5 inhibitors were better than placebo in improving

SEP2 in patients with DMED (WMD=21.24; 95% CI: 15.50 to 26.98; Figure 4, C) with no heterogeneity (P=0.627; I^2=0%), a fix effect model was used.

SEP3 means whether your erection can last long enough for you to have a successful intercourse. A total of 2 articles [22,23] were included in the literature comparing PDE5 inhibitors with placebo to improve SEP3 in patients with DMED. Meta-analysis showed that PDE5 inhibitors were better than placebo in improving SEP3 in patients with DMED (WMD=25.77; 95% CI: 18.78 to 32.77; Figure 4, D) with significant heterogeneity (P=0.003; I^2=88.9%), a random effect model was used.

GAQ

GAQ is a comprehensive index of male erectile function evaluation. A total of 7 articles [14,16-18,21-23] were included in the literature on the comparison of PDE5 inhibitors with placebo in improving GAQ in patients with DMED. Meta-analysis showed that PDE5 inhibitors were better than placebo in improving GAQ in patients with DMED (RR=2.98; 95% CI: 2.06 to 4.32; Figure 5) with significant heterogeneity (P<0.001; I^2=79.3%), a random effect model was used.

Safety

A total of 10 articles [14-20,22,23,25] were included in the literature concerning adverse events that occurred after DMED patients took the drug. Meta-analysis showed that PDE5 inhibitors had more adverse reactions (RR=3.35; 95% CI: 2.16 to 5.79), like flushing (RR=9.05; 95% CI: 4.18 to 19.61), headache (RR=4.68; 95% CI: 2.93 to 7.48), dyspepsia (RR=5.48; 95% CI: 2.83 to 10.63) than placebo. See more details in Table 2.

Discussion

With the changes in people's lifestyles and the aging process, the incidence of DM is increasing year by year, and more and more young adults are suffering from DM. [26] The various complications caused by DM seriously affect people's quality of life. ED is one of its common chronic complications and is easily overlooked when assessing DM conditions. [27] Normally, their NO will activate guanylate cyclase (GC) to convert GTP to second messenger cGMP, when males receive sexual stimulation. cGMP activates serine protein kinase, which further phosphorylates proteins and ion channels, leading to open potassium channels, hyperpolarization of muscle cell membranes, and intracellular calcium chelation of the endoplasmic reticulum. By inhibiting the calcium channel to block the calcium influx, the intracellular calcium concentration is reduced, the smooth muscle is relaxed, and the corpus cavernosum is filled with blood to induce penile erection. [28] Current studies shows that the damage of endothelial function is the possible pathogenesis of DMED. Diabetes can lead to complications such as peripheral vascular disease

and autonomic neuropathy. Endothelial cell-mediated smooth muscle relaxation and neurofibrillary neurogenic NOS (nNOS) activity is often the main cause of complications. In addition, some researches have demonstrated that decreased eNOS activity in endothelial cells leads to a reduction in NO level in penile blood vessels, which may result in DMED. [29] Oral type 5 phosphodiesterase (PDE5) inhibitors are the primary means of oral drug therapy for DMED. PDE5 inhibitors mainly increase the concentration of PDE5 by inhibiting the activity of PDE5, thereby enhancing the penile erectile function under sexual stimulation. [30]

This study retrieved RCTs from various PDE5 inhibitors for the treatment of DMED and systematically evaluated their efficacy and safety. This systematic review updated one RCT study, revised the data entry problem, and added new observation indexes such as sexual satisfaction evaluation and sexual self-confidence evaluation. The clinical efficacy evaluation method of ED is often carried out by means of subjective questionnaires. Currently, the most commonly used internationally is the IIEF-EF score questionnaire. In addition, SEP2 and SEP3 are also commonly used criteria for evaluating the clinical efficacy of ED. The study also included several other evaluation indicators, such as IIEF-Q3, IIEF-Q4, and GAQ. The results of this systematic review showed that there was a significant difference between the treatment group and the control group ($P < 0.001$), in the IIEF-EF score, IIEF-Q3, IIEF-Q4, SEP2, SEP3 and GAQ scores, suggesting that PDE5 inhibitors were significantly better than the control group in improving sexual desire, sexual life satisfaction. In terms of total adverse drug reactions, the difference between the treatment group and the control group was statistically significant, suggesting that the clinical complications should be noted to prevent the possibility of the above complications, like flushing, headache or dyspepsia.

However, this meta-analysis also had certain limitations: (1) due to the different types of PDE5 inhibitors used in the study, the subjects included in the study included different ethnic groups in Asia and Europe. In addition, some studies did not clearly distinguish the type of diabetes (T1DM or T2DM). Therefore, there is a certain heterogeneity. (2) The documents included in this article are all in English and are not included in the rest of the literature. At present, with the deepening of research, some scholars believe that ED is a chronic disease, requiring long-term use of PDE5 inhibitors, and studies have confirmed that tadalafil can be used to improve vascular endothelial function and improve erectile function to some extent; (3) the study included in the study did not mention the clinical efficacy of different modes of administration (on-demand and long-term use), pending more long-term and on-demand PDE5 inhibitors for the treatment of DMED randomized, double-blind, Multicenter clinical randomized controlled trial. In addition, this meta-analysis included some of the research funded by pharmaceutical manufacturers, so more real-world studies are needed to provide a clinical basis for PDE5 inhibitors to improve erectile function in patients with DMED.

Abbreviations

DM, diabetes mellitus; IIEF-EF, the erectile function scores of the International Index of Erectile Dysfunction; IIEF Q3, the question 3 of the International Index of Erectile Dysfunction; IIEF Q4, the

question 4 of the International Index of Erectile Dysfunction; SEP2, Sexual Encounter Profile Question 2; SEP3, Sexual Encounter Profile Question 3; RR, risk of ratio; CI, confidence interval; WMD, weighted mean difference; AE, adverse events; wk, weeks.

Declarations

Funding

The project is supported by National Natural Science Foundation of China (No. 81704086) and Young talents lifting project of China Association of Chinese Medicine (CACM-2018-QNRC2-C05).

Availability of data and materials

All data (literature) is available on Scopus, Embase, PubMed/Medline, Cochrane Library, PubMed, EMBASE, Cochrane library, Clinical Trials, China Knowledge Network (CNKI), Weipu Chinese Science and Technology Journal Full-text Database (VIP), Wanfang Data Resource System (WANFANG).

Author contributions

XL and QZ contributed equally to this work and are co-first authors. XL and JW designed the systematic review. QZ and JW drafted the protocol and JW and HD revised the manuscript. FC and YFL will independently screen the potential studies, extract data and finish data synthesis. BW, JW will assess the risk of bias. BW and HL will arbitrate any disagreement and ensure that no errors occur during the review.

Ethics approval and consent to participate

Not applicable. Our manuscript is a systematic review of previous studies; therefore it does not report on or involve the use of any animal or human data or tissue during our study.

Consent for publication

Not applicable. Our manuscript is a systematic review of previous studies;

therefore it does not contain any individual persons data obtained in our

study.

Competing interests

The authors declare that they have no competing interests

References

1. Pokharel Y, Tang F, Jones PG, et al. Adoption of the 2013 American College of Cardiology/American Heart Association Cholesterol Management Guideline in Cardiology Practices Nationwide. JAMA Cardiology. 2017;2(4): 361-369.
2. Kamenov ZA. A comprehensive review of erectile dysfunction in men with diabetes. Exp Clin Endocrinol Diabetes. 2015;123(03):141-158.
3. Eren AE, Ersay AR, Demirci E, et al. Diagnostic Value of Plasma Pentraxin3- Level For Diagnosis of Erectile Dysfunction. Urol J. 2018;15(4):199-203.
4. Ryan JG, Gajraj J. Erectile dysfunction and its association with metabolic syndrome and endothelial function among patients with type 2 diabetes mellitus. Journal of Diabetes & Its Complications. 2012;26(2):141-147.
5. Azmi S, Ferdousi M, Alam U, et al. Small-fibre neuropathy in men with type 1 diabetes and erectile dysfunction: a cross-sectional study. Diabetologia. 2017;60(6):1094-1101.
6. Henis O, Shahar Y, Steinvil A, et al. Erectile Dysfunction is Associated With Severe Retinopathy in Diabetic Men. Urology. 2011;77(5):1133-1136.
7. Castela Â, Costa C . Molecular mechanisms associated with diabetic endothelial-erectile dysfunction. Nature Reviews Urology. 2016;13(5):266.
8. Cellek S, Cameron NE, Cotter MA, et al. Pathophysiology of diabetic erectile dysfunction: potential contribution of vasa nervorum and advanced glycation endproducts. International Journal of Impotence Research. 2013;25(1):1-6.
9. Niitsuma M, Ichikawa T, Numakunia R, et al. Phosphodiesterase type 5 (PDE5) inhibitors in erectile dysfunction: the proper drug for the proper patient. J Sex Med. 2011;8(12):3418-3432.
10. Hatzimouratidis K, Salonia A, Adaikan G, et al. Pharmacotherapy for Erectile Dysfunction: Recommendations From the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2016;13(4):465-488.
11. Balhara YPS, Sarkar S, Gupta R. Phosphodiesterase-5 inhibitors for erectile dysfunction in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Indian J Endocrinol Metab. 2015;19(4):451-461.
12. Liu Q , Cai J , Lin L Z , et al. Efficacy and safety of phosphodiesterase inhibitors for erectile dysfunction in diabetic men: A meta-analysis. National Journal of Andrology. 2015;21(5):447.
13. Xiao Li, Qi Zhao, Jingshang Wang, et al. Efficacy and safety of PDE5 inhibitors in the treatment ofdiabetes mellitus erectile dysfunction: Protocol for a systematic review. Medicine (Baltimore). 2018;97(40):e12559.

14. Rendell MS, Rajfer J, Wicker PA, et al. Sildenafil for Treatment of Erectile Dysfunction in Men With Diabetes: A Randomized Controlled Trial. Jama. 1999;281(5):421-426.
15. Boulton AJ, Selam JL, Sweeney M, et al. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. Diabetologia. 2001;44(10):1296-1301.
16. IÑIGO SÁENZ, Anglin G, Knight JR et al. Effects of tadalafil on erectile dysfunction in men with diabetes. Journal of Urology. 2003;170(1):679-680.
17. Goldstein I, Young JM, Fischer J, et al. Vardenafil, a New Phosphodiesterase Type 5 Inhibitor, in the Treatment of Erectile Dysfunction in Men With Diabetes: A multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care. 2003;26(3):777-783.
18. Stuckey BG, Jadzinsky MN, Murphy LJ, et al. Sildenafil Citrate for Treatment of Erectile Dysfunction in Men With Type 1 Diabetes: Results of a randomized controlled trial. Diabetes Care. 2003;26(2):279-284.
19. Safarinejad MR. Oral sildenafil in the treatment of erectile dysfunction in diabetic men: A randomized double-blind and placebo-controlled study. Journal of Diabetes and its Complications. 2004;18(4):205-210.
20. Ziegler D, Merfort F, Ahlen HV, et al. Efficacy and Safety of Flexible-Dose Vardenafil in Men with Type 1 Diabetes and Erectile Dysfunction. Journal of Sexual Medicine. 2006;3(5):883-891.
21. Hatzichristou D, Gambla M, Rubio-Aurioles E, et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabetic medicine. 2008, 25(2):138-146.
22. Park HJ, Choi HK, Ahn TY, et al. Efficacy and safety of oral mirodenafil in the treatment of erectile dysfunction in diabetic men in Korea: A multicenter, randomized, double-blind, placebo-controlled clinical trial. J Sex Med. 2010;7:2842-2850.
23. 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;8:2048-2061.
24. Goldstein I, Jones LA, Belkoff LH, et al. Avanafil for the treatment of erectile dysfunction: A multicenter, randomized, double-blind study in men with diabetes mellitus. Mayo Clin Proc. 2012;87:843-852.
25. Santi D, Granata AR, Guidi A , et al. Six months of daily treatment with Vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: a randomized, double-blind, prospective trial. European Journal of Endocrinology. 2016;174:513-522.
26. Botha S, Forde L, Macnaughton S, et al. Effect of non-surgical weight management on weight and glycaemic control in people with type 2 diabetes: a comparison of interventional and non-interventional outcomes at 3 years. Diabetes Obesity & Metabolism, 2018, 20(4): 879-888.
27. Chung P H , Gehring C , Firoozabadi R , et al. Risk Stratification for Erectile Dysfunction after Pelvic Fracture Urethral Injuries. Urology, 2018;115:174-178.

28. Assaly, Rana, et al. Low intensity extracorporal shock waves therapy improves erectile function in diabetic type II rats independently of NO/cGMP pathway. Journal of Urology. 2016;196(3):950-956.
29. Liu P , Jiang J , Xia J , et al. Effect of Low Androgen Status on the Expression of P2Y Receptors in the Corpus Cavernosum of Rats. Urology. 2018;116:229.e1-229.e6.
30. Kniotek M, Boguska A. Sildenafil Can Affect Innate and Adaptive Immune System in Both Experimental Animals and Patients. J Immunol Res.

Tables

Table 1 Characteristics of the included studies on PDE-5 inhibitors for erectile dysfunction in men with diabetes mellitus (DM)

Study ID	Drug and dose	Cases	Mean ages	Nation	Type of DM	Outcomes	Treatment duration
Marc S 1999	Sildenafil 50-100 mg	268	T：57 C：57	US	T1 and T2	IIEF-EF, IIEF Q3, IIEF Q4, GAQ, AE	12wk
Boulton AJ 2001	sildinafil 25-100 mg	219	T：58.2 C：59.1	UK	T2	IIEF-EF, IIEF Q3, IIEF Q4, AE	12wk
IÑIGO SÁENZ 2002	tadalafil 10 mg/20 mg	218	T_1:55.50 T_2:55.47 C:54.8	Spain	T1 and T2	IIEF-EF, IIEF Q3, IIEF Q4, GAQ, AE	12wk
Goldstein I 2003	vardenafil 10 mg/20 mg	452	T_1:56.9 T_2:58.0 C:56.8	US, Canada	T1 and T2	IIEF-EF, GAQ, AE	12wk
Stuckey BG 2003	sildinafil 25-100 mg	188	T：46.8 C：47.8	Multiple countries	T1	GAQ, AE	12wk
Safarinejad MR 2004	sildinafil 100 mg	373	T：46 C：46	Iran	T1 and T2	IIEF Q3, IIEF Q4, AE	16wk
Ziegler D 2006	Vardenafil 5-25 mg	318	T：50.2 C：50.4	Germany	T1	IIEF-EF, SEP-2, AE	12wk
Hatzichristou D 2008	tadalafil 2.5 mg/5 mg	298	T_1:56 T_2:57 C:58	North America, Europe and Australia	T1 and T2	GAQ	12wk
Park HJ 2010	mirodenafil 100 mg	139	T：55.5 C：57.3	Korea	T1 and T2	IIEF-EF, IIEF Q3, IIEF Q4, SEP-2, SEP-3, GAQ, AE	12wk
Moondu G 2011	udenafil 200 mg/100 mg	225	T_1:54.44 T_2:55.47 C:54.89	Korea	T1 and T2	GAQ, AE	12wk
Goldstein I 2012	avanafil 100 mg/200 mg	390	T_1:59.0 T_2:58.2 C:58.2	US	T1 and T2	IIEF-EF, SEP-2, SEP-3	12wk
Santi D 2016	Vardenafil 10 mg	54	T：55.8 C：55.5	Italy	T2	IIEF-EF, AE	24wk

Table 2 Comparison of PDE5 inhibitors and placebo in adverse events.

Items	RR	95%Cl	I^2	P	Studies (N)
Adverse events (total)	3.35	2.16-5.79	85%	P<0.00001	10
Flushing	9.05	4.18-19.61	0%	P<0.00001	7
Headache	4.68	2.93-7.48	0%	P<0.00001	7
Dyspepsia	5.48	2.83-10.63	0%	P<0.00001	6

Abbreviations: CI, confidence interval; RR, risk ratio.

Figures

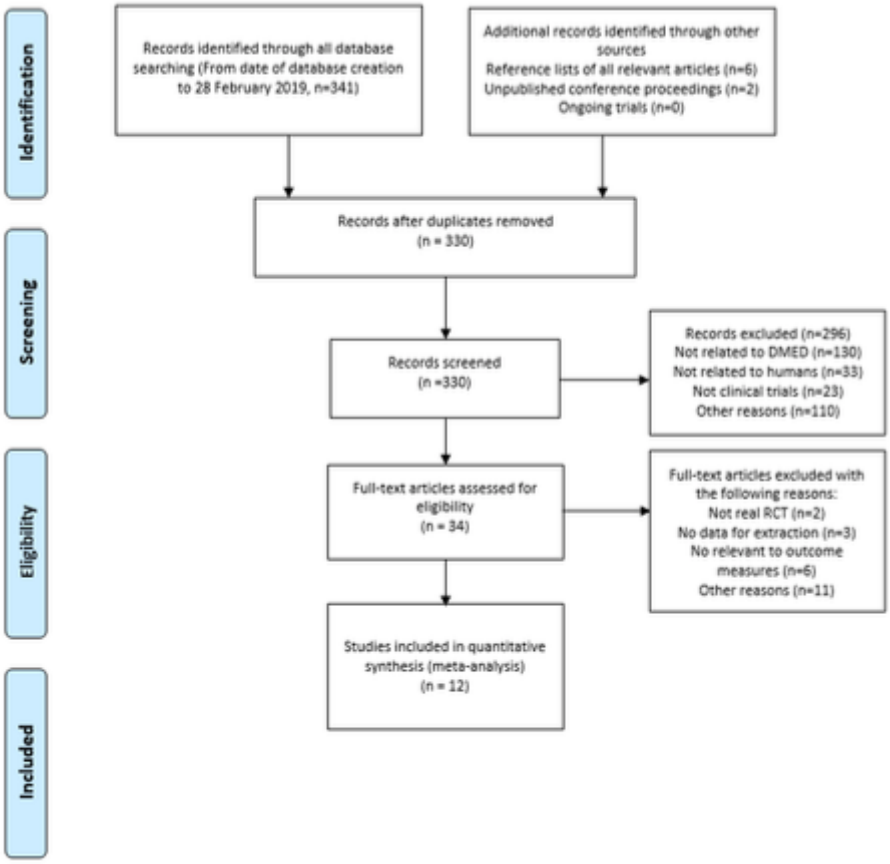

Figure 1

PSIMA Flow Chart

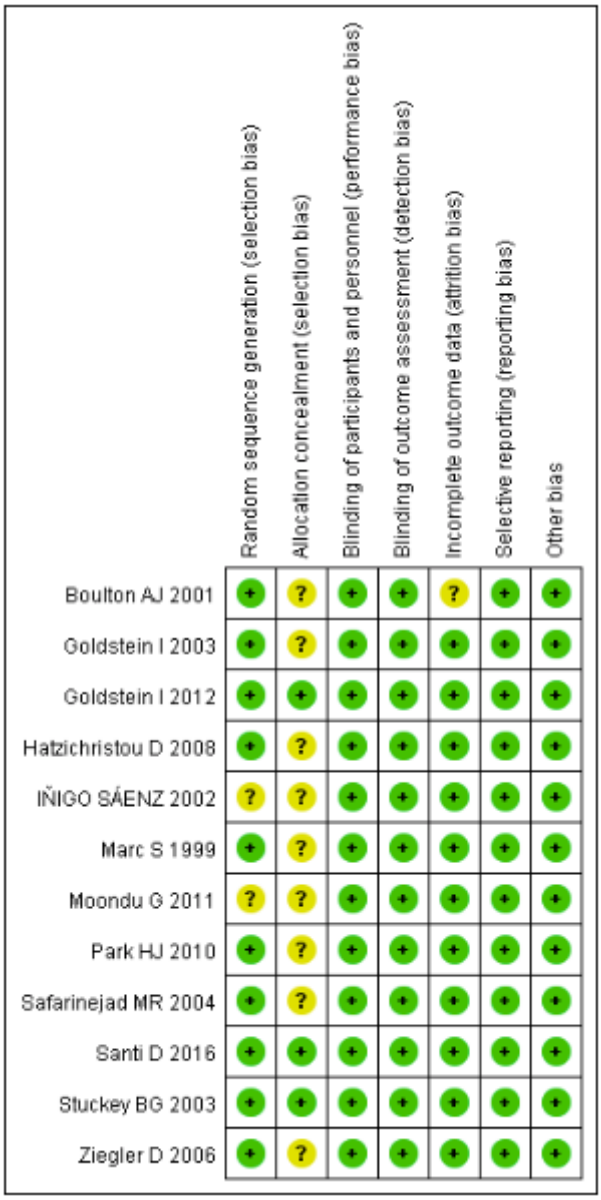

Figure 2

The risk of bias assessment of the studies

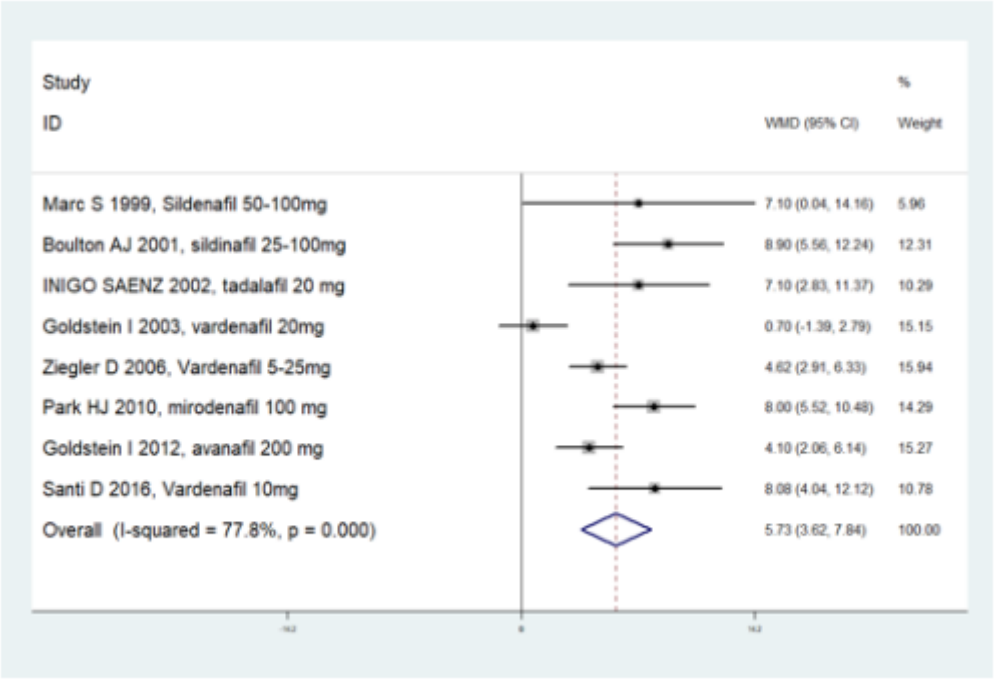

Figure 3

Forest plot for comparison of PDE5 inhibitors and placebo in IIEF-EF.

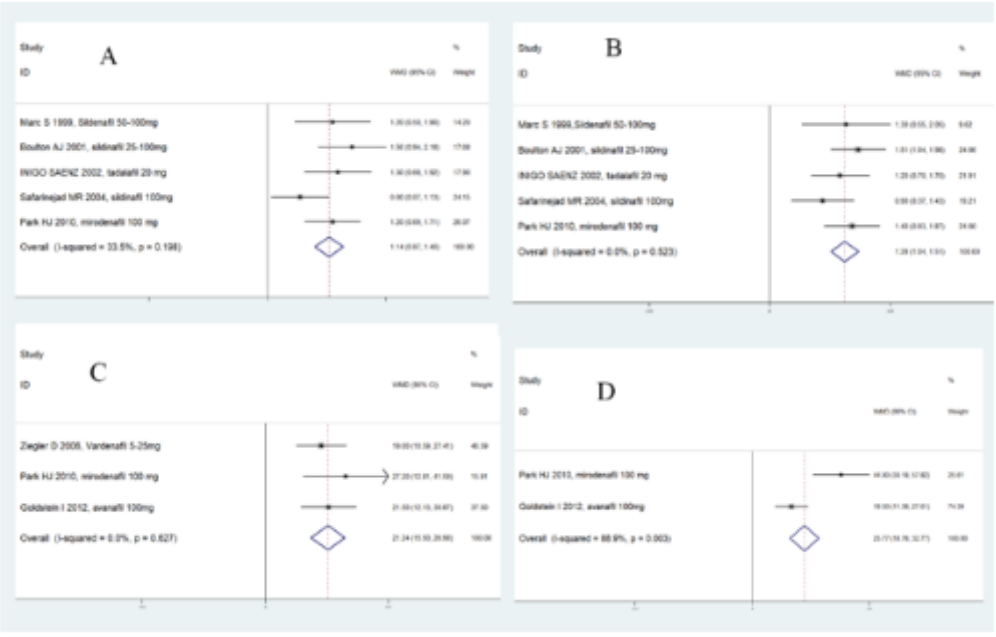

Figure 4

Forest plot for comparison of PDE5 inhibitors and placebo in index of sexual satisfaction. A. IIEF Q3. B. IIEF Q4. C. SEP2. D. SEP3

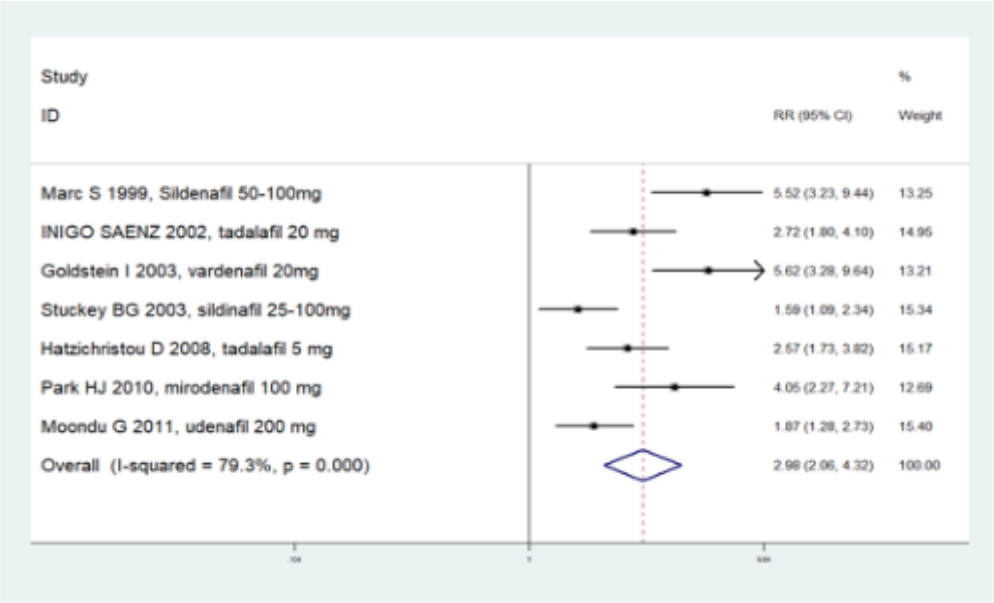
Study
ID
RR (95% CI)
%
Weight
Marc S 1999, Sildenafil 50-100mg
5.52 (3.23, 9.44)
13.25
INIGO SAENZ 2002, tadalafil 20 mg
2.72 (1.80, 4.10)
14.95
Goldstein I 2003, vardenafil 20mg
5.62 (3.28, 9.64)
13.21
Stuckey BG 2003, sildinafil 25-100mg
1.59 (1.09, 2.34)
15.34
Hatzichristou D 2008, tadalafil 5 mg
2.57 (1.73, 3.82)
15.17
Park HJ 2010, mirodenafil 100 mg
4.05 (2.27, 7.21)
12.69
Moondu G 2011, udenafil 200 mg
1.87 (1.28, 2.73)
15.40
Overall (I-squared = 79.3%, p = 0.000)
2.98 (2.06, 4.32)
100.00

Figure 5