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REVIEW

Comparative efficacy and safety of phosphodiesterase type 5 inhibitors for erectile dysfunction in diabetic men: a Bayesian network meta-analysis of randomized controlled trials

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Abstract

Purpose To compare the efficacy and safety profiles of different phosphodiesterase-5 inhibitors (PDE5Is) administrations for erectile dysfunction (ED) in diabetic men, including on-demand (PRN) and regular regimens (OAD).

Materials and methods Searches were carried out in four electronic databases: PubMed (until April 17th, 2017); Scopus (until April 17th, 2017); Embase (until April 17th, 2017); and Cochrane (until April 18th, 2017). The outcomes for this study are as follows: (1) Global Assessment Question (GAQ) positive response rate; (2) changes from baseline to the end of the study in Erectile Function Domain of International Index of Erectile Function (IIEF-EF); and (3) treatment-related adverse events (TRAEs). The comparative effects of PDE5I regimens were analyzed with random-effect models in a Bayesian Framework using the GeMTC R package.

Results We identified 1056 records, of which 15 randomized trials with 5274 patients were included. The included studies covered eight kinds of PDE5I administration: avanafil PRN; mirodenafil PRN; sildenafil PRN; tadalafil PRN; tadalafil OAD; udenafil PRN; udenafil OAD; vardenafil PRN; and placebo. In surface under the cumulative ranking curve analysis, vardenafil PRN ranked first, third and first, and mirodenafil PRN ranked second, first and second in GAQ, IIEF-EF, and TRAEs, respectively.

Conclusions PDE5I administrations were generally efficient and well-tolerated in diabetic men. Among these administrations, vardenafil PRN and mirodenafil PRN seem to have a possible advantage of efficacy and avoiding adverse effects compared to others. There is no significant difference between regular and on-demand regimens of PDE5Is.

Keywords Erectile dysfunction · Diabetes · Phosphodiesterase type 5 inhibitors · Network meta-analysis

Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance [1]. A greater risk of ED is strongly associated with diabetes [2]. The prevalence of ED in diabetic men has been reported to be 35–75% [3–7].

The pathophysiology of ED in diabetic men is multifactorial, and its main underlying causes fall into three classes: psychogenic, neurological, and vasogenic. Psychogenically, diabetes-associated depression may decrease libido and reduce the ability to have intercourse [8]. Neurologically, diabetes may cause sensory neuropathy, which reduces sexual stimulation that triggers the cognitive processes leading to an erection [9]. In the NO/cGMP (nitric oxide/cyclic guanosine monophosphate) signaling pathway of penile erection, the cavernosal nerve releases NO in response to

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sexual stimulation [10]. NO then stimulates the production of cGMP via interaction with guanylyl cyclase [11]. cGMP acts downstream as a second messenger, leading to penile erection. Given the reduced NO synthesis and impaired activity of guanylyl cyclase [12] in diabetic men, it is easier for such patients to experience erectile dysfunction, and erectile dysfunction is harder to cure.

Phosphodiesterase-5 inhibitors (PDE5Is), including avanafil, mirodenafil, sildenafil, tadalafil, vardenafil and udenafil are currently the first-line oral therapy for ED of any etiology [13]. The inhibition of PDE5I reduces the hydrolysis of cGMP in the cavernosal tissue, resulting in smooth muscle relaxation with increased arterial blood flow, which compresses the subtunical venous plexus, leading to penile erection [14]. However, in diabetic patients, the decrease in NO and impaired activity of guanylyl cyclase restricts the production of cGMP. Therefore, PDE5Is might not be as effective for treating diabetic ED as they are for treating non-diabetic ED, as shown by several studies [15].

Traditionally, PDE5Is are prescribed as on-demand regimens (PRN) and taken 15–30 min before intercourse. Recently, however, some studies showed that the regular regimens (OAD) of PDE5Is yielded higher treatment satisfaction for patients [16, 17]. Further, animal studies have shown that PDE5I OAD significantly improves or prevents intracavernous structural alterations due to aging, diabetes, or surgical damage [18, 19]. However, no data are available for humans. Tadalafil 2.5 and 5 mg once-daily for ED were approved by the European Medicines Agency in 2007. As an alternative to on-demand regimens, the regular dosing regimens afforded by PDE5Is allow couples to have spontaneous and more frequent sexual activity because dosing time and time of sexual activity do not have to coincide [20].

We aim to compare different administrations of PDE5Is and different regimens for diabetic ED. Ideally, all PDE5I administrations for diabetic ED should be evaluated via direct comparisons in high-quality studies, but to date, no data exist comparing different PDE5Is for diabetic ED directly. A systematic review and network meta-analysis (NMA) is one feasible way of combining evidence of direct and indirect comparisons simultaneously.

Evidence acquisition

Data source and search strategy

The study protocol was registered in PROSPERO, CRD42017062264 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017062264). Searches were

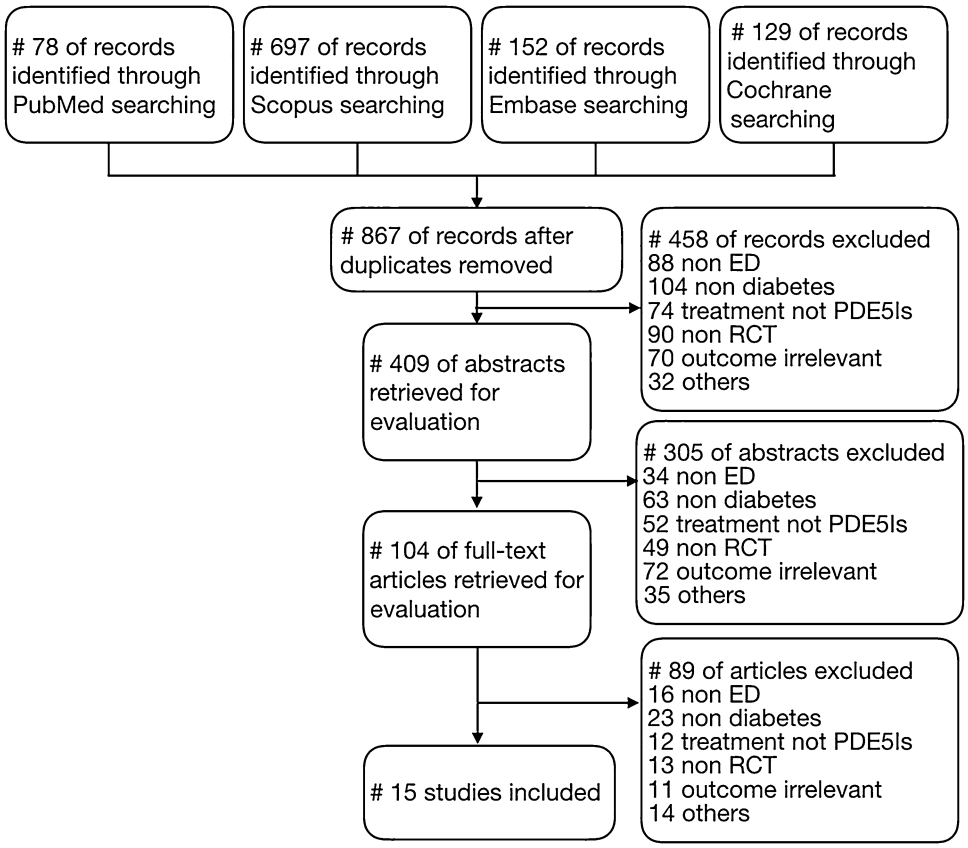
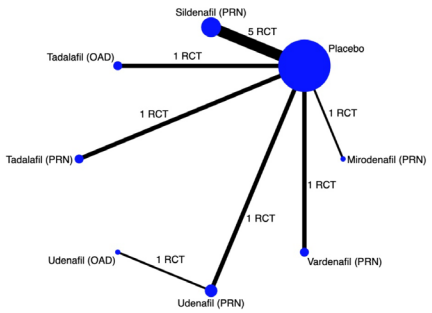


Fig. 1 Flowchart of study selection. *ED* Erectile dysfunction, *PDE5Is* phosphodiesterase type 5 inhibitors, *RCT* randomized controlled trial

Table 1 Estimates of effects (with 95% credible intervals) and confidence ratings for comparisons of PDE5Is for the treatment of erectile dysfunction in diabetic men on the outcome Global Assessment Question (GAQ) positive response rate

Outcome: GAQ

Patients: diabetic men with erectile dysfunction
Interventions: mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil OAD, udenafil PRN, udenafil OAD, vardenafil PRN
Comparisons: placebo
Outcomes: GAQ



#13 RCTs, 2149 patients	Comparator							
	Mirodenafil PRN	**Sildenafil PRN**	**Tadalafil OAD**	**Tadalafil PRN**	**Udenafil OAD**	**Udenafil PRN**	**Vardenafil PRN**	**Placebo**
Mirodenafil PRN	NA	OR 0.61 (0.16, 2.2)	OR 0.32 (0.08, 1.28)	OR 0.31 (0.07, 1.31)	OR 0.62 (0.08, 4.86)	OR0.45 (0.11, 1.96)	OR0.91 (0.21, 3.66)	OR 0.07 (0.02, 0.23)
	NA	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[1]
Sildenafil PRN	OR 1.64 (0.45, 6.15)	NA	OR 0.52 (0.22, 1.23)	OR 0.52 (0.21, 1.26)	OR 1.02 (0.2, 5.82)	OR 0.75 (0.29, 1.94)	OR 1.48 (0.62, 3.56)	OR 0.12 (0.07, 0.19)
	⊕◯◯◯ Very low[1,2,3]	NA	⊕⊕◯◯ Low[1,2]	⊕⊕◯◯ Low[1,2]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[1,2]	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[1]
Tadalafil OAD	OR 3.12 (0.78, 13.2)	OR 1.92 (0.81, 4.51)	NA	OR 0.99 (0.36, 2.8)	OR 1.96 (0.35, 12.07)	OR 1.43 (0.49, 4.23)	OR 2.83 (1.04, 7.81)	OR 0.22 (0.11, 0.45)
	⊕⊕⊕◯ Moderate[1]	⊕⊕◯◯ Low[1,2]	NA	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]
Tadalafil PRN	OR 3.19 (0.76, 13.5)	OR 1.93 (0.79, 4.71)	OR 1.01 (0.36, 2.82)	NA	OR 1.96 (0.34, 12.24)	OR 1.45 (0.48, 4.4)	OR 2.86 (1, 8.14)	OR 0.22 (0.1, 0.47)
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	NA	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕⊕ High
Udenafil OAD	OR 1.62 (0.21, 11.93)	OR 0.98 (0.17, 5.11)	OR 0.51 (0.08, 2.86)	OR 0.51 (0.08, 2.91)	NA	OR 0.73 (0.18, 2.84)	OR 1.45 (0.23, 8.12)	OR 0.11 (0.02, 0.54)
	⊕⊕◯◯ Low[2,3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	NA	⊕⊕⊕◯ Moderate3	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[3]
Udenafil PRN	OR 2.2 (0.51, 9.51)	OR 1.34 (0.51, 3.43)	OR 0.7 (0.24, 2.02)	OR 0.69 (0.23, 2.08)	OR 1.36 (0.35, 5.71)	NA	OR 1.98 (0.67, 5.79)	OR 0.15 (0.07, 0.34)
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[3]	NA	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕⊕ High
Vardenafil PRN	OR 1.1 (0.27, 4.67)	OR 0.67 (0.28, 1.62)	OR 0.35 (0.13, 0.96)	OR 0.35 (0.12, 1)	OR 0.69 (0.12, 4.27)	OR 0.5 (0.17, 1.49)	NA	OR 0.08 (0.04, 0.16)
	⊕⊕⊕◯ Moderate[3]	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕◯ Moderate[2]	NA	⊕⊕⊕⊕ High
Placebo	OR 14.22 (4.32, 49.26)	OR 8.66 (5.37, 14.12)	OR 4.53 (2.24, 9.25)	OR 4.48 (2.12, 9.63)	OR 8.86 (1.85, 46.86)	OR 6.47 (2.93, 14.74)	OR 12.86 (6.27, 26.49)	NA
	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕◯ Moderate[1]	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	NA

GRADE Working Group grades of evidence—high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate

OR Odds ratio, *PRN* on-demand regimen (pro-re-nata), *OAD* regular regimen (once a day)

[1]Certainty lowered for risk of bias

Table 1 (continued)

[2]Certainty lowered for indirectness

[3]Certainty lowered for imprecision

carried out in four electronic databases: PubMed (until April 17th, 2017); Scopus (until April 17th, 2017); Embase (until April 17th, 2017); and Cochrane (until April 18th, 2017). There was no limitation on language or publication, and the search strategies included MeSH terms and keywords for 'erectile dysfunction', 'diabetes', 'phosphodiesterase type 5 inhibitors', and a specific filter for clinical trials. The full versions of search strategies for the four databases are in Supplement 1. Records identified through electronic searching were checked manually.

Study selection

Randomized clinical trials (RCTs) that compared PDE5Is and placebo or various PDE5I regimens in the diabetic population were identified. The inclusion criteria were as follows: (1) RCTs that studied patients with reported erectile dysfunction for at least 3 months; (2) RCTs that studied patients with diabetes for at least 3 months; (3) RCTs that studied treatment with PDE5Is for 6–16 weeks; and (4) placebo-controlled studies or head-to-head trials in which different oral PDE5I administrations were compared. The exclusion criteria were as follows: (1) non-randomized studies; and (2) studies in which PDE5Is were combined with other drugs (e.g., losartan, folic acid, undecanoate, etc.). The outcomes for this study are as follows: (1) Global Assessment Question positive response rate (GAQ: Has the treatment you have been taking improved your erections?); (2) changes from baseline to the end of the study in the Erectile Function domain of the International Index of Erectile Function [21] (IIEF-EF, the total score of the 1st, 2nd, 3rd, 4th, 5th, and 15th questions of the International Index of Erectile Function, score range 1–30); and (3) treatment-related adverse events (TRAEs), including headache, flushing, dyspepsia, respiratory tract disorder, distorted vision, dizziness and nausea, which are the most common adverse effects of PDE5Is. Liao and Qiu independently evaluated study eligibility by their titles, abstracts, and full-text articles. Wei resolved discrepancies.

Data extraction and quality assessment

Liao and Bao independently extracted data from studies that met the inclusion and exclusion criteria mentioned above. The data extracted included study characteristics (title, author, publication year, study design), patient characteristics (age, type of diabetes, duration of erectile dysfunction and diabetes), intervention (type of PDE5I and dosage), outcomes (mean, standard deviation, number of patients for continuous data, number of positive responses and total number of patients for dichotomous data). The calculator in RevMan 5.3 was used to convert data, such as standard error and p value, to the standard deviation and combine data from subgroups when needed. Authors of studies with needed missing data were contacted when necessary.

The methodological quality of included studies was appraised with the Cochrane Collaboration bias appraisal tool [22]. The quality of evidence on all comparisons was evaluated by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [23].

Data synthesis and analysis

The comparative effects of PDE5I regimens were analyzed with random-effect models in a Bayesian Framework using the GeMTC R package [24]. In the Bayesian hierarchical model provided by the GeMTC package, prior distributions can be set automatically for the treatment effects compared with placebo, the study baseline effects, and the heterogeneity in random effects models. And all direct and indirect comparisons were exploited to generate a consistent estimate of all interventions, thus allowing calculation of the ranked probabilities of interventions.

Summarized effect size was calculated as the mean difference (MD) for continuous data and as the odds ratio (OR) for dichotomous data, together with 95% confidence intervals (CIs). Heterogeneity among studies in each comparison was assessed with a Chi-squared test and I2 value [22]. Absolute effects were calculated. The surface under the cumulative ranking curve (SUCRA) of each treatment was generated to rank efficacy and safety of all PDE5I administrations in the diabetic men. Based on cumulative probability plots, an intervention that always ranked first would have a SUCRA value of one, whereas an intervention that always ranked last would have a value of zero [25].

SUCRA values were also plotted in a scatter diagram to identify the administrations with the best balance between efficacy and safety (GAQ & IIEF-EF for efficacy ranking, GAQ & TRAEs for efficacy-adverse-effect balance) [26].

An inconsistency assessment was performed where direct and indirect evidence were combined.

Table 2 Estimates of effects (with 95% credible intervals) and confidence ratings for comparisons of PDE5Is for the treatment of erectile dysfunction in diabetic men on the outcome changes from baseline to the end of the study in Erectile Function Domain of International Index of Erectile Function (IIEF-EF)

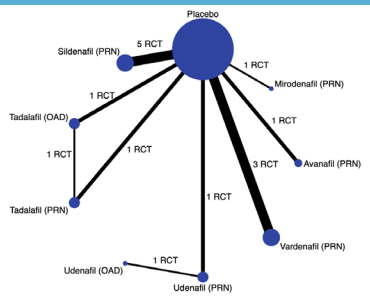
Outcome: IIEF-EF

Patients: diabetic men with erectile dysfunction

Interventions: Avanafil PRN, mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil OAD, udenafil PRN, udenafil OAD, vardenafil PRN

Comparisons: placebo

Outcomes: IIEF-EF



#15 RCTs, 5274 patients	Comparator								
	Avanafil PRN	**Mirodenafil PRN**	**Placebo**	**Sildenafil PRN**	**Tadalafil OAD**	**Tadalafil PRN**	**Udenafil OAD**	**Udenafil PRN**	**Vardenafil PRN**
Avanafil PRN	NA	MD 4.77 (1.11, 8.48)	MD -3.1 (-5.08, -1.17)	MD 2.39 (0.06, 5.07)	MD 1.15 (-1.57, 3.87)	MD 1.54 (-1.14, 4.83)	MD 2.32 (-2.72, 7.5)	MD 3.16 (-0.02, 6.41)	MD 2.46 (0.06, 4.92)
	NA	⊕⊕◯◯ Low[2,3]	⊕⊕⊕⊕ High	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]
Mirodenafil PRN	MD -4.77 (-8.48, -1.11)	NA	MD -7.89 (-11.02, -4.8)	MD -2.36 (-5.74, 1.23)	MD -3.66 (-7.32, -0.05)	MD -3.22 (-6.8, 0.87)	MD -2.41 (-8.19, 3.24)	MD -1.64 (-5.65, 2.39)	MD -2.3 (-5.72, 1.09)
	⊕⊕◯◯ Low[2,3]	NA	⊕⊕⊕◯ Moderate[3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]
Placebo	MD 3.1 (1.17, 5.08)	MD 7.89 (4.8, 11.02)	NA	MD 5.53 (4.04, 7.23)	MD 4.23 (2.37, 6.09)	MD 4.67 (2.68, 7.23)	MD 5.46 (0.73, 10.21)	MD 6.26 (3.48, 8.85)	MD 5.58 (4.15, 7.07)
	⊕⊕⊕⊕ High	⊕⊕⊕◯ Moderate[3]	NA	⊕⊕⊕◯ Moderate[1]	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕⊕ High	⊕⊕⊕⊕ High
Sildenafil PRN	MD -2.39 (-5.07, -0.06)	MD 2.36 (-1.23, 5.74)	MD -5.53 (-7.23, -4.04)	NA	MD -1.29 (-3.84, 1.07)	MD -0.86 (-3.38, 1.97)	MD -0.09 (-5.13, 4.86)	MD 0.75 (-2.39, 3.71)	MD 0.04 (-2.21, 2.15)
	⊕⊕◯◯ Low[1,2]	⊕◯◯◯ Very low[1,2,3]	⊕⊕⊕◯ Moderate[1]	NA	⊕⊕◯◯ Low[1,2]	⊕⊕◯◯ Low[1,2]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[1,2]	⊕⊕◯◯ Low[1,2]
Tadalafil OAD	MD -1.15 (-3.87, 1.57)	MD 3.66 (0.05, 7.32)	MD -4.23 (-6.09, -2.37)	MD 1.29 (-1.07, 3.84)	NA	MD 0.36 (-1.11, 2.79)	MD 1.24 (-3.89, 6.3)	MD 2.03 (-1.17, 5.2)	MD 1.33 (-1, 3.71)
	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[1]	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[1,2]	NA	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]
Tadalafil PRN	MD -1.54 (-4.83, 1.14)	MD 3.22 (-0.87, 6.8)	MD -4.67 (-7.23, -2.68)	MD 0.86 (-1.97, 3.38)	MD -0.36 (-2.79, 1.11)	NA	MD 0.79 (-4.71, 5.8)	MD 1.59 (-2.01, 4.76)	MD 0.93 (-2.05, 3.34)
	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕⊕ High	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	NA	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]
Udenafil OAD	MD -2.32 (-7.5, 2.72)	MD 2.41 (-3.24, 8.19)	MD -5.46 (-10.21, -0.73)	MD 0.09 (-4.86, 5.13)	MD -1.24 (-6.3, 3.89)	MD -0.79 (-5.8, 4.71)	NA	MD 0.84 (-3.2, 4.88)	MD 0.15 (-4.82, 5.02)
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	NA	⊕⊕⊕◯ Moderate[3]	⊕⊕◯◯ Low[2,3]
Udenafil PRN	MD -3.16 (-6.41, 0.02)	MD 1.64 (-2.39, 5.65)	MD -6.26 (-8.85, -3.48)	MD -0.75 (-3.71, 2.39)	MD -2.03 (-5.2, 1.17)	MD -1.59 (-4.76, 2.01)	MD -0.84 (-4.88, 3.2)	NA	MD -0.69 (-3.62, 2.3)
	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕⊕ High	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[3]	NA	⊕⊕⊕◯ Moderate[2]
Vardenafil PRN	MD -2.46 (-4.92, -0.06)	MD 2.3 (-1.09, 5.72)	MD -5.58 (-7.07, -4.15)	MD -0.04 (-2.15, 2.21)	MD -1.33 (-3.71, 1)	MD -0.93 (-3.34, 2.05)	MD -0.15 (-5.02, 4.82)	MD 0.69 (-2.3, 3.62)	NA
	⊕⊕⊕◯ Moderate[2]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕⊕ High	⊕⊕◯◯ Low[1,2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[2]	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕◯ Moderate[2]	NA

Table 2 (continued)

GRADE Working Group grades of evidence—high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate

MD Mean difference, *PRN* on-demand regimen (pro-re-nata), *OAD* regular regimen (once a day)

[1]Certainty lowered for risk of bias

[2]Certainty lowered for indirectness

[3]Certainty lowered for imprecision

Results

Search results and study characteristics

In total, 1056 records in four databases were identified, of which 952 were excluded after an evaluation of titles and abstracts. A total of 104 full-text articles were retrieved, and 15 studies [27–41] with 5274 patients were included (Fig. 1). The baseline characteristics of included studies are summarized in Supplement 2. The included studies covered eight kinds of PDE5I administration: avanafil PRN; mirodenafil PRN; sildenafil PRN; tadalafil PRN; tadalafil OAD; udenafil PRN; udenafil OAD; vardenafil PRN; and placebo. The dosage of each PDE5I for the included studies was within the recommended range.

GAQ

Eleven studies [29–34, 36–39, 41], including eight different administrations of PDE5Is (mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil OAD, udenafil PRN, udenafil OAD, vardenafil PRN, and placebo), informed the analysis of the GAQ (2149 patients). PDE5Is of all kinds were significantly more effective than placebo in improving the GAQ positive response rate. These results demonstrate that a higher GAQ outcome is associated with vardenafil PRN compared to tadalafil PRN (64% vs. 60%; OR 2.8; 95% CI 1.0–8.0) and tadalafil OAD (64% vs. 57%; OR 2.8; 95% CI 1.0–7.7) (Table 1). SUCRA analysis suggested that vardenafil PRN and mirodenafil PRN have the highest probability of a positive response in diabetic ED patients, with SUCRA values of 0.828 and 0.825, respectively.

IIEF-EF

Fifteen studies [27–41], including nine different administrations of PDE5Is (avanafil PRN, mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil OAD, udenafil PRN, udenafil OAD, vardenafil PRN, and placebo), informed the analysis of the IIEF-EF (5274 patients). Compared with avanafil PRN, the following were more effective in improving IIEF: mirodenafil PRN (9.30 vs. 4.95; MD: 4.8; 95% CI 1.0–8.6); sildenafil PRN (7.07 vs. 4.95; MD: 2.5; 95% CI 0.058–5.1); and vardenafil PRN (8.04 vs. 4.95; MD: 2.5; 95% CI 0.031–5.0) (Table 2). SUCRA analysis suggested that mirodenafil PRN has the highest probability of improving the IIEF-EF (SUCRA: 0.93).

TRAEs

Thirteen studies [27–31, 33–35, 37–41], including eight different classes of PDE5Is (mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil OAD, udenafil PRN, vardenafil PRN, and placebo), informed the analysis of TRAEs (4985 patients). The TRAEs of PDE5Is in diabetic men were generally mild. These included headache, flushing, dyspepsia, respiratory tract disorder, distorted vision, dizziness and nausea (Supplement 5). The safety of different administrations was similar, except that sildenafil PRN showed a significant increase in TRAEs compared with vardenafil PRN (6.0% vs. 35.3%; OR 3.6; 95% CI 1.2–12) (Table 3). SUCRA analysis suggested that vardenafil PRN has the highest probability of avoiding TRAEs in diabetic ED patients, with a SUCRA value of 0.66.

OAD vs. PRN

A total of five studies [28, 32, 34, 36, 39] (1551 patients) informed this analysis. No significant difference was found between two regimens of PDE5Is in either efficacy or safety profile (Fig. 2). Compared with tadalafil PRN, tadalafil OAD showed no better efficacy in the GAQ (OR 0.99; 95% CI 0.35–2.9) or IIEF-EF (MD − 0.41; 95% CI − 2.9 to 1.2), nor did it cause more TRAEs (OR 1.1; 95% CI 0.28–4.5). Further, udenafil OAD performed no better than udenafil PRN in improving the GAQ (OR 0.99; 95% CI 0.35–2.9) or IIEF-EF (MD − 0.75; 95% CI − 4.9 to 3.3).

Table 3 Estimates of effects (with 95% credible intervals) and confidence ratings for comparisons of PDE5Is for the treatment of erectile dysfunction in diabetic men on the outcome treatment-related adverse events (TRAEs)

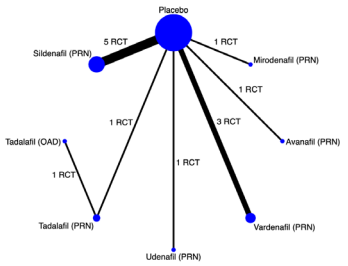
Outcome: TRAEs

Patients: diabetic men with erectile dysfunction

Interventions: avanafil PRN, mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil OAD, udenafil PRN, vardenafil PRN

Comparisons: placebo

Outcomes: TRAEs



#13 RCTs, 4985 patients	Comparator							
	Avanafil PRN	**Mirodenafil PRN**	**Placebo**	**Sildenafil PRN**	**Tadalafil OAD**	**Tadalafil PRN**	**Udenafil PRN**	**Vardenafil PRN**
Avanafil PRN	NA	OR 0.01 (-2.46, 2.55)	OR -1.22 (-2.94, 0.41)	OR 1.17 (-0.68, 3.01)	OR 0.94 (-1.79, 3.68)	OR 0.84 (-1.52, 3.2)	OR 0.82 (-1.78, 3.69)	OR -0.11 (-2, 1.74)
	NA	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]
Mirodenafil PRN	OR -0.01 (-2.55, 2.46)	NA	OR -1.23 (-3.14, 0.54)	OR 1.16 (-0.87, 3.12)	OR 0.94 (-1.93, 3.75)	OR 0.83 (-1.69, 3.27)	OR 0.79 (-1.91, 3.77)	OR -0.12 (-2.19, 1.85)
	⊕⊕◯◯ Low[2,3]	NA	⊕⊕⊕◯ Moderate[3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]
Placebo	OR 1.22 (-0.41, 2.94)	OR 1.23 (-0.54, 3.14)	NA	OR 2.39 (1.68, 3.18)	OR 2.17 (0.02, 4.36)	OR 2.06 (0.43, 3.76)	OR 2.02 (0.12, 4.39)	OR 1.11 (0.28, 1.98)
	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕◯ Moderate[3]	NA	⊕⊕⊕◯ Moderate[1]	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕⊕ High	⊕⊕⊕◯ Moderate[3]	⊕⊕⊕⊕ High
Sildenafil PRN	OR -1.17 (-3.01, 0.68)	OR -1.16 (-3.12, 0.87)	OR -2.39 (-3.18, -1.68)	NA	OR -0.22 (-2.54, 2.07)	OR -0.33 (-2.16, 1.49)	OR -0.38 (-2.43, 2.09)	OR -1.28 (-2.42, -0.16)
	⊕◯◯◯ Very low[1,2,3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕⊕◯ Moderate[3]	NA	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[1,2]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[1,2]
Tadalafil OAD	OR -0.94 (-3.68, 1.79)	OR -0.94 (-3.75, 1.93)	OR -2.17 (-4.36, -0.02)	OR 0.22 (-2.07, 2.54)	NA	OR -0.11 (-1.51, 1.29)	OR -0.13 (-3.04, 3.03)	OR -1.06 (-3.37, 1.28)
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[3]	⊕◯◯◯ Very low[1,2,3]	NA	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]
Tadalafil PRN	OR -0.84 (-3.2, 1.52)	OR -0.83 (-3.27, 1.69)	OR -2.06 (-3.76, -0.43)	OR 0.33 (-1.49, 2.16)	OR 0.11 (-1.29, 1.51)	NA	OR -0.03 (-2.59, 2.83)	OR -0.95 (-2.82, 0.9)
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕⊕ High	⊕⊕◯◯ Low[1,2]	⊕⊕◯◯ Low[2,3]	NA	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[2]
Udenafil PRN	OR -0.82 (-3.69, 1.78)	OR -0.79 (-3.77, 1.91)	OR -2.02 (-4.39, -0.12)	OR 0.38 (-2.09, 2.43)	OR 0.13 (-3.03, 3.04)	OR 0.03 (-2.83, 2.59)	NA	OR -0.91 (-3.39, 1.18)
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕◯ Moderate[3]	⊕◯◯◯ Very low[1,2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	NA	⊕⊕◯◯ Low[2,3]
Vardenafil PRN	OR 0.11 (-1.74, 2)	OR 0.12 (-1.85, 2.19)	OR -1.11 (-1.98, -0.28)	OR 1.28 (0.16, 2.42)	OR 1.06 (-1.28, 3.37)	OR 0.95 (-0.9, 2.82)	OR 0.91 (-1.18, 3.39)	NA
	⊕⊕◯◯ Low[2,3]	⊕⊕◯◯ Low[2,3]	⊕⊕⊕⊕ High	⊕⊕◯◯ Low[1,2]	⊕⊕◯◯ Low[2,3]	Moderate2	⊕⊕◯◯ Low[2,3]	NA

Table 3 (continued)

GRADE Working Group grades of evidence—high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality: we are very uncertain about the estimate

OR Odds ratio, *PRN* on-demand regimen (pro-re-nata), *OAD* regular regimen (once a day)

[1]Certainty lowered for risk of bias

[2]Certainty lowered for indirectness

[3]Certainty lowered for imprecision

SUCRA

The scatter diagram of the SUCRA analysis (Fig. 3) was plotted with a SUCRA value for the GAQ on the *y*-axis and a SUCRA value for IIEF-EF on the *x*-axis. Mirodenafil PRN, PRN, sildenafil PRN, and udenafil OAD showed higher SUCRA values for each of the two efficacy outcomes than did the other administrations.

The scatter diagram of the SUCRA analysis (Fig. 4) was plotted with a SUCRA value for the GAQ on the *y*-axis and a SUCRA value for TRAEs on the *x*-axis. Vardenafil PRN and mirodenafil PRN showed higher SUCRA values for both efficacy and adverse effect than did other administrations, showing them to be safer and more effective.

Network assumptions, quality assessment, grade of evidence

Among all outcomes, there was a loop of three pairwise comparisons. No inconsistency between direct and indirect evidence was significant (Fig. 5).

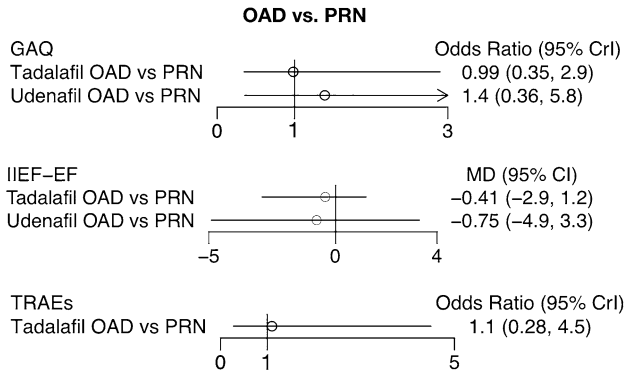


Fig. 2 Comparisons of regular regimen (OAD) with on-demand dosage (PRN) of different phosphodiesterase type 5 inhibitors for diabetic erectile dysfunction in Global Assessment Question (GAQ), International Index of Erectile Function-Erectile Function Score (IIEF-EF), treatment-related adverse events (TRAEs). *CrI* Credible interval, *MD* mean difference, *PRN* on-demand regimen (pro-re-nata), *OAD* regular regimen (once a day). No significant difference was noted in any comparison

We evaluated the literature using the Cochrane Collaboration bias appraisal tool [22] (Fig. 6). The overall methodological quality of the included randomized controlled trials was moderate.

The test of heterogeneity in NMA was generally low or moderate, excluding vardenafil PRN vs. placebo in TRAEs (Supplement 3).

We used the GRADE approach to evaluate the certainty in the direct and indirect evidence. The grades of evidence were mostly moderate to low due to the limited number of studies and indirectness (Tables 1, 2 and 3).

Sensitivity analysis

In a sensitivity analysis, we included only studies using the highest dosage of each compound. A total of eleven studies [27, 30, 32–40] (3505 patients) informed this analysis. The regimens included in the sensitivity analysis were as follows: tadalafil (PRN 20 mg; OAD 5 mg/day); udenafil (PRN 200 mg; OAD 50 mg/day); avanafil (PRN 200 mg); mirodenafil (PRN 100 mg); vardenafil (PRN 20 mg); and sildenafil (PRN 100 mg). The additional sensitivity analysis showed similar results to the main meta-analysis for both efficacy and adverse effects (Supplement 4).

Discussion

There were four major findings in our study. (1) PDE5Is were generally more efficient in improving erectile function and overall sex life satisfaction than was placebo for patients with diabetes. (2) Based on NMA and SUCRA analysis, vardenafil PRN and mirodenafil PRN have a possible advantage over other PDE5Is in terms of efficacy and avoiding adverse effects; no significant difference was found when comparing these two. (3) A daily regimen of PDE5I does not outperform on-demand regimen in efficacy or avoiding TRAEs. (4) PDE5Is were overall safe and well-tolerated by diabetic patients.

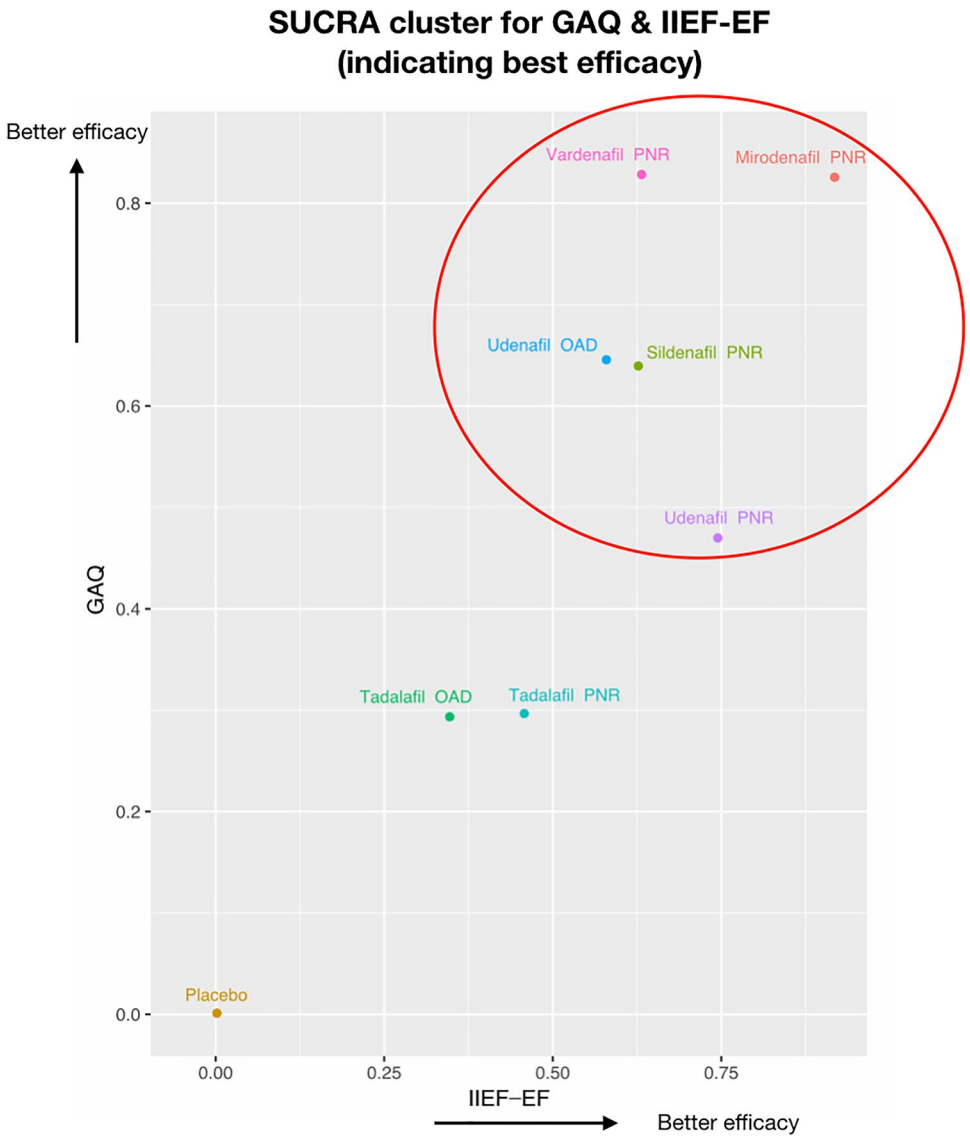


Fig. 3 Scatter plot including surface under cumulative ranking curve (SUCRA) value for Global Assessment Question (GAQ) on the *y*-axis and SUCRA value for International Index of Erectile Function-Erectile Function Score (IIEF-EF) on the *x*-axis. A higher SUCRA ranking for GAQ and IIEF-EF (on upper-right corner) indicates better efficacy. *PRN* On-demand regimen (pro-re-nata), *OAD* regular regimen (once a day)

To our knowledge, this is the first NMA that compares efficacy and safety of different PDE5I administrations for ED in diabetic men. Such comparison provides the best estimates of treatment outcomes by synthesizing all the available evidence and by highlighting potentially important differences in the IIEF-EF, GAQ, and TRAEs among all types of regimens.

The efficacy and safety of PDE5Is has been demonstrated in the broad-spectrum population in a previous systematic review and meta-analysis [42]. Moreover, some studies have demonstrated PDE51 efficacy and safety in patients with ED and other comorbidities, such as hypertension [43] and depression [44]. In this study, however, we limited the study population to a specific cohort of patients with diabetic ED.

A recently published traditional systematic review [45] comparing PDE5I and placebo for diabetic ED concluded that PDE5Is are generally effective and safe for ED in diabetic men. However, this review did not evaluate the comparative efficacy and safety profile of PDE5Is, nor did it distinguish OAD from PRN regimens. Our study proved that PDE5Is are well-tolerated and effective for improving the erectile function of diabetic patients. Further, we compared different PDE5Is given either on demand or on a daily basis. Only two PDE5Is, tadalafil and udenafil, have been given on

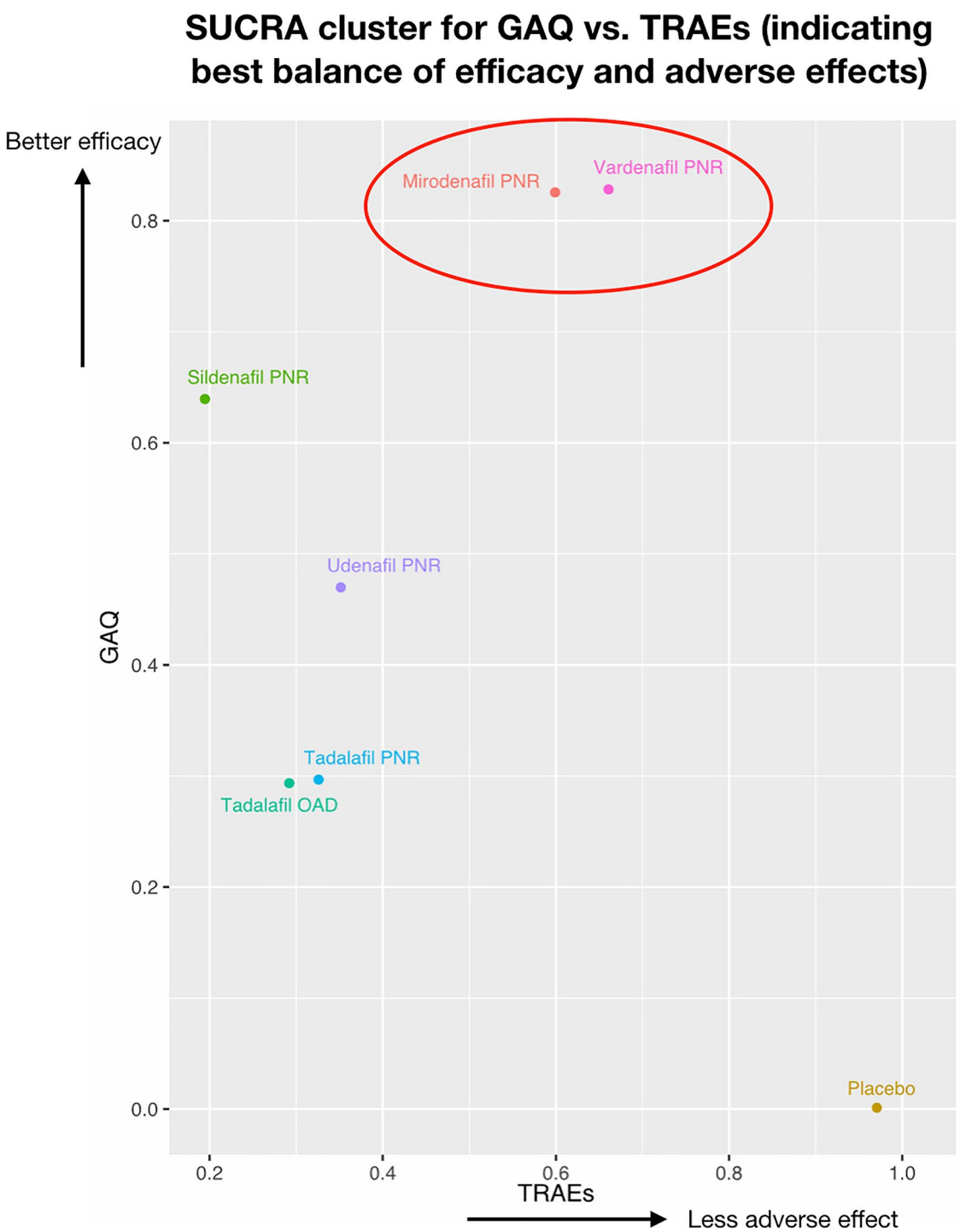


Fig. 4 Scatter plot including surface under cumulative ranking curve (SUCRA) value for Global Assessment Question (GAQ) on the *y*-axis and SUCRA value for treatment-related adverse events (TRAEs) on the *x*-axis. A higher SUCRA ranking for GAQ indicates better efficacy whereas a higher SUCRA ranking for TRAEs indicates fewer events associated with treatment. Cluster analysis demonstrates vardenafil PRN and mirodenafil PRN to be treatments with well-balanced efficacy and safety profile. *PRN* On-demand regimen (pro-re-nata), *OAD* regular regimen (once a day)

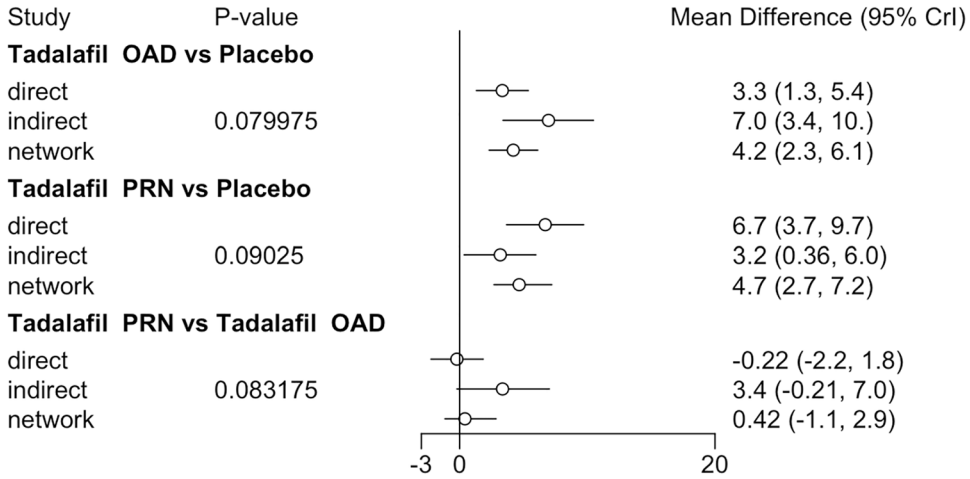


Fig. 5 Test of assumption of consistency. No inconsistency of direct and indirect evidence was noted with p value > 0.05. *CrI* Credible interval, *PRN* On-demand regimen (pro-re-nata), *OAD* regular regimen (once a day)

a daily basis for diabetic ED in RCTs, and only two studies have directly compared daily and on-demand regimens in this field. By integrating direct and indirect evidence, we found no significant difference between these two types of regimens. Another previous NMA [42] comparing oral on-demand PDE5Is among the general population suggested that tadalafil is the most effective agent, followed by vardenafil. In our study, however, neither tadalafil PRN nor OAD is proven to be superior to other administrations. This discrepancy could be caused by the fact that our study population differs. In our study, vardenafil PRN and mirodenafil PRN seem to have the best efficacy–safety balance.

Even though all dosages in this NMA were within clinical recommendation, the efficacy and safety profile can be affected by the PDE5I dosage. However, directly adjusting for dosage might not be appropriate. For instance, the maximum dose of sildenafil is 100 mg on demand, while that of tadalafil is 20 mg. To account for this, we performed an additional sensitivity analysis, in which we included only the maximum dosages of a PDE5I if various dosages had been reported. The sensitivity analysis showed similar results to our main network meta-analysis. Administration of PDE5Is, whether OAD or PRN, showed significant improvement in IIEF and GAQ, and vardenafil and mirodenafil PRN seemed to have a better balance of efficacy and safety compared with other PDE5Is.

The present study has several limitations. First, relative to the number of PDE5I administrations evaluated (Tables 1, 2 and 3), the number of studies is limited. Second, we did not perform an NMA of some other related outcomes, such as SEP2, SEP3, and the percentage of patients who achieved IIEF-EF scores > 26, due to differential and incomplete reporting of outcomes within the literature. Third, the study populations differ across different studies, as some PDE5Is were studied only among Caucasian populations while some were studied only among East Asian populations.

Conclusions

In conclusion, PDE5I administrations were generally efficient and well-tolerated in diabetic men. Among these administrations, vardenafil PRN and mirodenafil PRN seem to have a possible advantage of efficacy and avoiding adverse effects compared to others. There is no significant difference between regular and on-demand regimens of PDE5Is. However, given the limited number of studies in this field, conclusions should be interpreted with caution. Future head-to-head RCTs are needed to confirm or disprove our present findings.

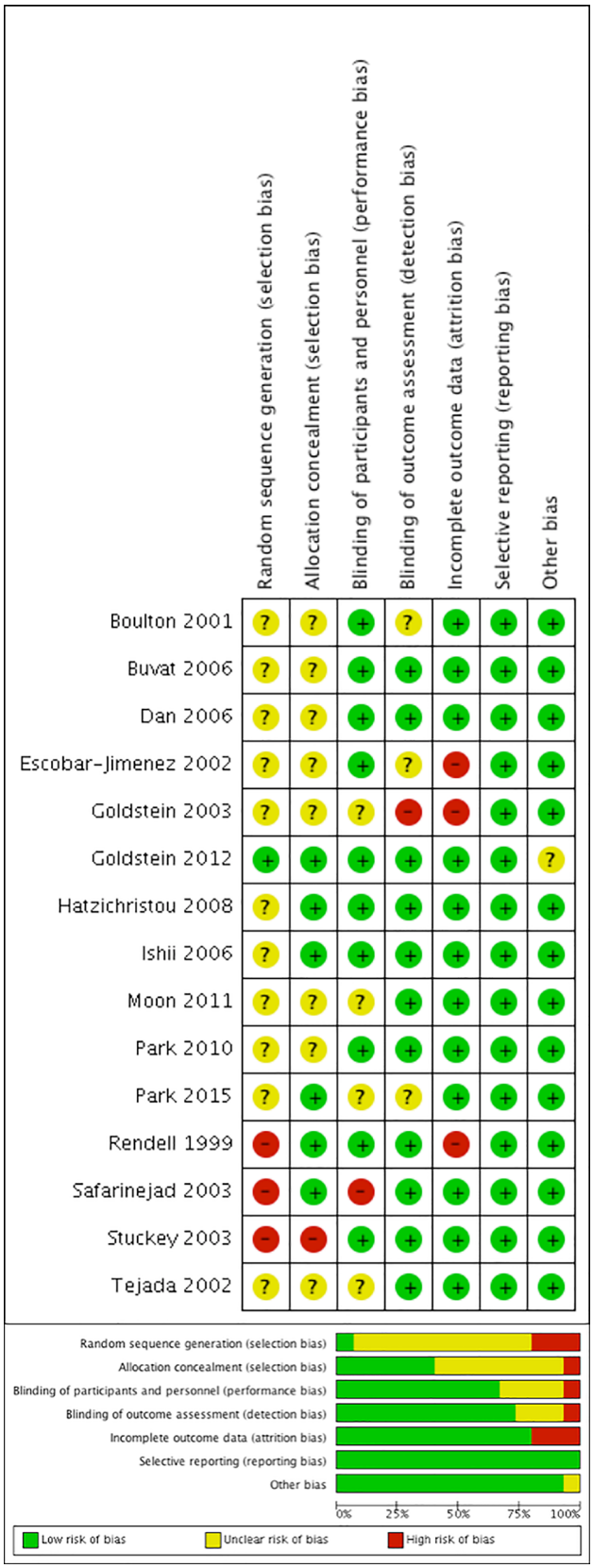


Fig. 6 Risk of bias summary and risk of bias graph: review authors' judgements about each risk of bias item for each included study and each item presented as percentages across all included studies

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