

Efficacy and Safety of Udenafil for Erectile Dysfunction: A Meta-analysis of Randomized Controlled Trials

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OBJECTIVE	To systematically review the evidence on the efficacy and safety of udenafil as treatment of erectile dysfunction from randomized controlled trials.
METHODS	We searched PubMed, Embase, and the Cochrane Library database up to October 2011. The outcome measures assessed were the change from baseline for the International Index of Erectile Function erectile function domain score (primary), the change from baseline for Sexual Encounter Profile questions 2 and 3, the shift to normal rate (erectile function domain ≥ 26), the response to the Global Assessment Questionnaire and adverse effects (secondary). Two of us independently assessed the study quality and extracted data. All data were analyzed using Review Manager, version 5.0.2.
RESULTS	Five randomized controlled trials totaling 1109 patients were included. At the follow-up endpoints, udenafil was found to be more effective than placebo, and the tolerability was good. The pooled results showed that the udenafil group was significantly greater than the placebo group in the change from baseline for the International Index of Erectile Function erectile function domain score (mean difference 5.65, 95% confidence interval 4.41-6.89, $P < .00001$). All included studies indicated that most adverse events were mild or moderate in severity, and no serious adverse events were reported during the study period. The most common drug-related adverse events were flushing and headache (udenafil vs placebo, 5.6% vs 1.8% and 3.1% vs 0%, respectively).
CONCLUSION	The results from the current meta-analysis have suggested that udenafil is an effective and well-tolerated therapy for erectile dysfunction. The findings of the present review highlight the need for more efficient performance of higher quality, large-sample, various-race, long-term, randomized controlled trials to verify the efficacy and safety of udenafil. UROLOGY 80: 134-139, 2012. © 2012 Elsevier Inc.

Erectile dysfunction (ED) is defined as a man's consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity.¹ ED often affects patients' physical and psychosocial health and has a significant effect on the quality of life of patients and their partners and families. Epidemiologic studies have suggested that the incidence of moderate to severe ED is approximately 5%-20% of men.^{2,3} For ED,

the common risk factors are cardiovascular disease⁴ and diabetes,⁵ except for radical prostatectomy.

Currently, numerous strategies have been used to overcome ED. The treatment options for ED include oral medications, psychological management, vacuum constriction devices, intracavernosal injections, transurethral drug delivery, penile prostheses, vascular surgery, and discontinuation of medications that can cause ED.⁶ Men have reported a clear preference for oral medications, which are considered first-line therapy for those who do not have a specific contraindication to their use. Three phosphodiesterase type 5 inhibitors (PDE5-Is), sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis), have been introduced in the management of ED. As is well known, the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)/cGMP-dependent protein kinase I pathway serves as the principal regulatory basis for penile erection.⁷ Accordingly, selective inhibition of PDE5, which catalyzes the degradation of cGMP, is the essential mechanism underlying the action of sildenafil.⁸

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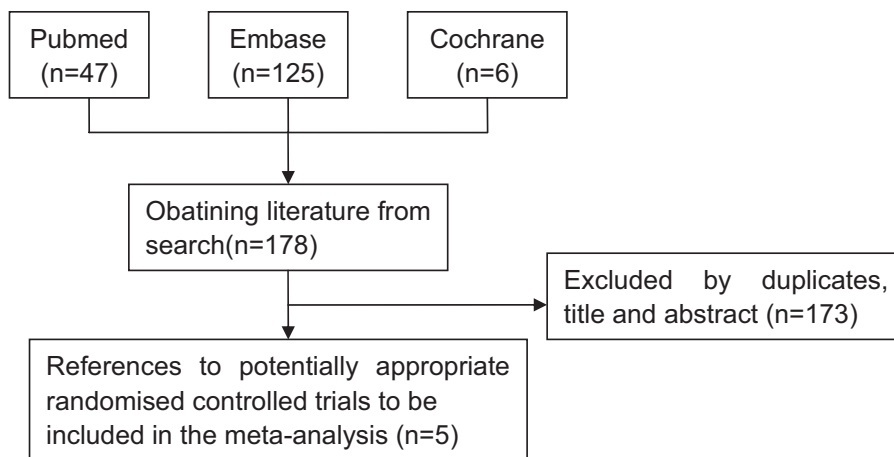


Figure 1. Flow chart for selecting randomized controlled trials for analysis.

In recent years, a new oral selective PDE5-I, udenafil (Zydena, Dong-A, Seoul, Korea), has been developed for the treatment of ED. Its pharmacokinetic profiles include a time to reach a peak plasma concentration (Tmax) of 1.0-1.5 hours and a half-life of 11-13 hours, which would confer unique clinical properties of both relatively rapid onset and long duration of action.⁹ Moreover, the isoenzyme selectivity profile of udenafil is similar to that of sildenafil. Several randomized controlled trials have reported the clinical effectiveness and safety of udenafil for ED. However, to date, no systematic review and meta-analysis, including randomized controlled trials, have been performed to determine the effectiveness and safety of udenafil for ED. Therefore, this meta-analysis was performed to evaluate the efficacy and safety of udenafil for patients with ED to provide more reliable evidence for the use of udenafil.

MATERIAL AND METHODS

We reviewed the following databases to obtain relevant studies of udenafil: PubMed, Embase, and the Cochrane Library. The following search terms were used: (“udenafil” OR “Zydena” OR “DA 8159”) AND (“Erectile Dysfunction” OR “Impotence”). We also searched the references of included studies to identify additional potentially relevant studies. Only 1 randomized controlled trial was identified in which patients were randomized to receive either udenafil or placebo for ED. No language restrictions were used. The titles and abstracts were screened independently by 2 reviewers, who discarded the studies that were not applicable, and 2 reviewers independently assessed the retrieved titles and abstracts of all identified trials to confirm fulfillment of the inclusion criteria. Data extraction was performed independently by the same investigators using standard data extraction forms. To reduce bias, 1 of the reviewers was unaware of the source of the publication and the authors’ names. Disagreements were resolved in consultation with the third reviewers. The quality of the included randomized trials was assessed using the Cochrane Collaboration tool.¹⁰

Our primary outcome was the change from baseline for the International Index of Erectile Function (IIEF) erectile function domain (EFD) score. The secondary outcomes were the change from baseline for Sexual Encounter Profile (SEP) ques-

tions 2 and 3, the shift to a normal rate (EFD ≥ 26), the response to the Global Assessment Questionnaire (GAQ), and adverse effects.

Statistical Analysis

We analyzed the data using Review Manager, version 5.0 (The Cochrane Collaboration, <http://ims.cochrane.org/revman>), and extracted and pooled the data for summary estimates. $P < .05$ was considered statistically significant. For the meta-analysis, we combined the data on dichotomous outcomes using the Mantel-Haenszel relative risk method. For continuous outcomes, we used the inverse variance weighted mean difference (MD) method and 95% confidence intervals (CIs). We used the chi-square statistic to assess the heterogeneity between the trials and the I^2 statistic to assess the extent of inconsistency. We used a fixed-effects model for calculations of summary estimates and their 95% CI, unless significant heterogeneity was present, in which case, the results were confirmed using a random effects statistical model. When significant heterogeneity was present, a sensitivity analysis was used to explore the reliability of the results. If the data were not depicted using the mean \pm standard deviation, the standard deviation was estimated using the statistical method.¹⁰ When data were available and sufficient, a subgroup analysis was performed to explore possible heterogeneity by the doses of udenafil and the etiology of ED.

RESULTS

The combined search strategies identified 5 randomized controlled trials, including 1109 patients (561 in the udenafil group and 548 in the placebo group), that met the inclusion criteria (Fig. 1). All studies¹¹⁻¹⁵ were multicenter, double-blind, randomized, placebo-controlled, parallel-group study and came from Korea. Three studies¹³⁻¹⁵ used 100 and 200 mg udenafil; one study¹² used 100 mg udenafil; one study¹¹ used 25, 50, and 75 mg udenafil. The study duration ranged from 4 to 12 weeks. Three studies reported the change from baseline for the IIEF EFD score, the change from baseline for SEP questions 2 and 3, the shift to a normal rate (EFD ≥ 26), and the response to the GAQ. One study reported the change from baseline for the IIEF EFD score, the change from

Table 1. Baseline characteristics of included studies

Study, Year	Intervention (n)	Mean Age (y)	ED Duration (y)	Previous PDE5-I Use (%)	Follow-Up (wk)	Outcome Measure
Paick et al, ¹³ 2008	Placebo (n = 54)	55.7 ± 7.4	3.2 ± 2.4	74.07	12	Change from baseline for IIEF EFD score, SEP Q2 and Q3, response to GAQ, adverse events
	Udenafil 100 mg (n = 57)	53.6 ± 7.5	3.5 ± 2.7	75.44		
	Udenafil 200 mg (n = 56)	54.6 ± 7.3	3.9 ± 3.1	82.14		
Paick et al, ¹⁴ 2009	Placebo (n = 55)	55.51 ± 8.25	4.33 ± 3.51	50.9	12	Change from baseline for IIEF EFD score, SEP Q2 and Q3, shift to normal rate, response to GAQ, adverse events
	Udenafil 100 mg (n = 53)	56.23 ± 8.24	4.06 ± 3.04	54.7		
	Udenafil 200 mg (n = 57)	55.89 ± 7.17	3.93 ± 3.53	57.9		
Park et al, ¹² 2010	Placebo (n = 51)	52.24 ± 9.56	3.4 ± 4.4	58.82	4	Change from baseline for IIEF EFD score, SEP Q2 and Q3, shift to normal rate, adverse events
	Udenafil 100 mg (n = 53)	53.57 ± 9.39	3.5 ± 3.9	71.7		
Moon et al, ¹⁵ 2011	Placebo (n = 57)	54.89 ± 8.18	3.67 ± 2.93	57.9	12	Change from baseline for IIEF EFD score, SEP Q2 and Q3, shift to normal rate, response to GAQ, adverse events
	udenafil 100 mg (n = 58)	55.47 ± 8.54	3.48 ± 2.47	56.9		
	udenafil 200 mg (n = 59)	54.44 ± 7.92	3.22 ± 2.83	59.3		
Zhao et al, ¹¹ 2011	Placebo (n = 60)	55.13 ± 9.50	None	71.7	12	Change from baseline for IIEF EFD score, SEP Q2 and Q3, shift to normal rate, response to GAQ, adverse events
	Udenafil 25 mg (n = 59)	59.71 ± 7.01		78.0		
	Udenafil 50 mg (n = 60)	57.62 ± 7.96		81.7		
	Udenafil 75 mg (n = 60)	56.20 ± 7.51		88.3		

ED, erectile dysfunction; PDE5-I, phosphodiesterase type 5 inhibitor; SEP, sexual encounter profile; Q, question; GAQ, global assessment question; IIEF, International Index of Erectile Function.

Table 2. Methodologic quality of included studies

Entry	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	ITT Analysis
Paick et al, ¹³ 2008	Unclear	Unclear	Double-blind	Yes	Unclear	Unclear	Yes
Paick et al, ¹⁴ 2009	Unclear	Unclear	Double-blind	Yes	Unclear	Unclear	Yes
Park et al, ¹² 2010	Unclear	Unclear	Double-blind	Yes	Unclear	Unclear	Yes
Moon et al, ¹⁵ 2011	Unclear	Unclear	Double-blind	Yes	Unclear	Unclear	Yes
Zhao et al, ¹¹ 2011	Unclear	Unclear	Double-blind	Yes	Unclear	Unclear	Yes

ITT, intention to treat.

baseline for SEP questions 2 and 3, and the shift to a normal rate (EFD ≥ 26). Another study reported the IIEF EFD score, the change from baseline for SEP questions 2 and 3, and the response to the GAQ. The characteristics and quality assessment of the 5 studies are summarized in Tables 1 and 2. Compared with placebo, the results of the meta-analysis for the efficacy of udenafil for ED are summarized in Table 3.

Primary Endpoint: Change From Baseline for IIEF EFD Score

Five studies reported the change from baseline for the IIEF EFD score. Heterogeneity was observed in pooled analysis ($P < .0001$, $I^2 = 75\%$). Thus, we performed meta-analysis using the random-effects model. The

pooled results showed that the udenafil group was significantly greater than the placebo group in the change from baseline for the IIEF EFD score (MD 5.65, 95% CI 4.41-6.89, $P < .00001$). Subsequently, subgroup analysis was performed to explore possible heterogeneity.

Four studies reported the use of 100 mg udenafil for ED. After deleting the duration of treatment < 12 weeks,¹² the pooled results of the following 3 studies showed there was still statistical significance for the change from baseline for the IIEF EFD score in the udenafil group and placebo group (fixed-effects model, MD 6.69, 95% CI 5.09-8.29, $P < .00001$). Three studies reported the use of 200 mg udenafil for ED. The pooled results demonstrated there was still statistical significance for the change from baseline for the IIEF EFD score in the

Table 3. Results of meta-analysis for the efficacy of udenafil for erectile dysfunction compared with placebo

Parameter	n	Sample Size (I/C)	Heterogeneity	Pooled MD or RR (95% CI)	Z Test P Value
Change from baseline in IIEF erectile function domain score	5	561/548	$\chi^2 = 35.43, P < .0001, I^2 = 75\%$	5.65 (4.41-6.89)	8.95, < .00001
100 mg	3	163/160	$\chi^2 = .65, P = .72, I^2 = 0\%$	6.69 (5.09-8.29)	8.22, < .00001
200 mg	3	167/160	$\chi^2 = 1.69, P = .43, I^2 = 0\%$	8.62 (6.83-10.42)	9.42, < .00001
Hypertension	2	188/171	$\chi^2 = 6.33, P = .18, I^2 = 37\%$	5.69 (3.90-7.47)	6.26, < .00001
Diabetes mellitus	2	166/167	$\chi^2 = 11.87, P = .02, I^2 = 66\%$	4.06 (1.44-6.69)	3.03, .002
Change from baseline for SEP Q2	5	561/548	$\chi^2 = 31.19, P = .0003, I^2 = 71\%$	22.14 (14.77-29.51)	5.89, < .00001
100 mg	3	163/160	$\chi^2 = 1.31, P = .52, I^2 = 0\%$	26.60 (18.17-35.04)	6.18, < .00001
200 mg	3	167/160	$\chi^2 = .64, P = .72, I^2 = 0\%$	32.43 (22.75-42.10)	6.57, < .00001
Change from baseline for SEP Q3	5	561/548	$\chi^2 = 16.65, P = .05, I^2 = 46\%$	31.22 (25.90-36.55)	11.49, < .00001
100 mg	3	163/160	$\chi^2 = 1.14, P = .56, I^2 = 0\%$	36.02 (25.82-46.22)	6.92, < .00001
200 mg	3	167/160	$\chi^2 = 1.14, P = .56, I^2 = 0\%$	47.61 (34.13-61.10)	6.92, < .00001
Shift to normal rate	4	451/440	$\chi^2 = 7.97, P = .34, I^2 = 12\%$	3.44 (2.50-4.72)	7.62, < .00001
100 mg	3	160/157	$\chi^2 = 2.94, P = .23, I^2 = 32\%$	4.30 (2.47-7.51)	5.14, < .00001
200 mg	2	113/106	$\chi^2 = 2.84, P = .09, I^2 = 65\%$	5.23 (2.83-9.67)	5.28, < .00001
Response to GAQ	4	504/497	$\chi^2 = 8.03, P = .43, I^2 = 0\%$	2.37 (2.07-2.70)	12.85, < .00001
100 mg	3	163/160	$\chi^2 = 2.99, P = .22, I^2 = 33\%$	2.32 (1.83-2.95)	6.87, < .00001
200 mg	3	164/160	$\chi^2 = 3.16, P = .21, I^2 = 37\%$	2.64 (2.09-3.33)	8.22, < .00001

I, intervention; C, control; MD, mean difference; RR, risk ratio; CI, confidence interval; SEP, Sexual Encounter Profile; Q, question; GAQ, Global Assessment Question; IIEF, International Index of erectile Function.

udenafil group and placebo group (fixed-effects model, MD 8.62, 95% CI 6.83-10.42, $P < .00001$).

Two studies evaluated the efficacy of udenafil for the treatment of ED in hypertensive men. The pooled results showed that the udenafil group was superior to placebo group in the change from baseline for the IIEF EFD score (MD 5.58, 95% CI 4.17-6.98, $P < .00001, I^2 = 37\%$). Also, 2 studies evaluated the efficacy of udenafil for the treatment of ED with diabetes mellitus. The pooled results showed that the udenafil group was superior to the placebo group in the change from baseline for the IIEF EFD score (MD 4.06, 95% CI 1.44-6.69, $P = .002, I^2 = 66\%$).

Secondary Endpoints

Change From Baseline for SEP Questions 2. Five studies reported the change from baseline for SEP question 2. Heterogeneity was observed in the pooled analysis ($P = .0003, I^2 = 71\%$). The pooled results showed that the udenafil group was also significantly greater than placebo group in the change from baseline for SEP question 2 (MD 22.14, 95% CI 14.77-29.51, $P < .00001$). After deleting those with a duration of treatment of <12 weeks,¹² the pooled results of the following 3 studies still showed statistical significance for the change from baseline for SEP question 2 in the 100-mg udenafil group and placebo group (fixed-effects model, MD 26.60, 95% CI 18.17-35.04, $P < .00001$). Three studies reported the use of 200 mg udenafil for ED. The pooled results demonstrated that there was still statistical significance for the change from baseline for SEP question 2 in the 200-mg udenafil group and placebo group (fixed-effects model, MD 32.43, 95% CI 22.75-42.10, $P < .00001$).

Change From Baseline for SEP Question 3. Five studies reported the change from baseline for SEP questions 3. There was no significant heterogeneity in the pooled analysis ($P = .05, I^2 = 46\%$). The pooled results showed that the udenafil group was also significantly greater than in the placebo group in the change from baseline for SEP question 3 (MD 31.22, 95% CI 25.90-36.55, $P < .00001$). After deleting those with a duration of treatment of <12 weeks,¹² the pooled results of the following 3 studies still showed statistical significance for the change from baseline for SEP question 3 in the 100-mg udenafil group and placebo group (fixed-effects model, MD 36.02, 95% CI 25.82-46.22, $P < .00001$). Three studies reported the use of 200 mg udenafil for ED. The pooled results demonstrated that there was still statistical significance for the change from baseline for SEP question 3 in the 200-mg udenafil group and placebo group (fixed-effects model, MD 47.61, 95% CI 34.13-61.10, $P < .00001$).

Shift to Normal Rate (EFD ≥ 26). Four studies reported the shift to a normal rate (EFD ≥ 26). No significant heterogeneity was found in the pooled analysis ($P = .34, I^2 = 12\%$). The pooled results showed that the udenafil group was also significantly greater than the placebo group in the shift to a normal rate (EFD ≥ 26 ; risk ratio [RR] 3.75, 95% CI 2.80-5.03, $P < .00001$). Three studies reported the use of 100 mg udenafil for ED. The pooled results showed there was still statistical significance for the change from baseline for the shift to normal rate (EFD ≥ 26) in the 100-mg udenafil group and placebo group (fixed-effects model, RR 4.30, 95% CI 2.47-7.51, $P < .00001$). Three studies reported the use of 200 mg

ildenafil for ED. The pooled results demonstrated there was still statistical significance for the change from baseline for SEP question 3 in the 200-mg sildenafil group and placebo group (random-effects model, RR 5.71, 95% CI 1.60-20.43, $P = .007$).

Response to GAQ. Four studies reported the response to the GAQ. No significant heterogeneity was found in the pooled analysis ($P = .43$, $I^2 = 0\%$). The pooled results showed that the sildenafil group was also significantly greater than the placebo group in the response to the GAQ (RR 2.37, 95% CI 2.07-2.70, $P < .00001$). Three studies reported the use of 100 mg sildenafil for ED. The pooled results showed that there was still statistical significance for the response to the GAQ in the 100-mg sildenafil group and placebo group (fixed-effects model, RR 2.32, 95% CI 1.83-2.95, $P < .00001$). Three studies reported the use of 200 mg sildenafil for ED. The pooled results demonstrated that there was still statistical significance for the response to the GAQ in the 200-mg sildenafil group and placebo group (fixed-effect model, RR 2.64, 95% CI 2.09-3.33, $P < .00001$).

Adverse Effects

All included studies indicated that most adverse events were mild or moderate in severity, and no serious adverse events were reported during the study period. The most common drug-related adverse events were flushing and headache. Two studies reported the incidence of flushing and headache within a study duration of 12 weeks (sildenafil vs placebo, 5.6% vs 1.8%, $P = .02$, $I^2 = 0\%$; 3.1% vs 0%, $P = .03$, $I^2 = 0\%$, respectively).

COMMENT

To our knowledge, this is first meta-analysis to evaluate the efficacy and safety of sildenafil for ED. As a new oral PDE5-I, sildenafil is a pyrazolopyrimidinone derivative with a molecular weight of 516.66.⁹ In the Phase I and II study, the results demonstrated that sildenafil was efficacious in 55% of patients with ED 8-12 hours after administration, and sildenafil treatment produced a highly significant improvement in ejection fraction, with up to a 91% vaginal penetration success rate.¹³ Our pooled results demonstrated that sildenafil can significantly improve the ED of patients, including the IIEF erectile function domain score, SEP questions 2 and 3, the shift to normal rate (EFD ≥ 26), and the response to the GAQ, with no serious adverse events during the study period. The most common drug-related adverse events were flushing and headache compared with placebo.

Nonadrenergic-noncholinergic nerves in the penis release NO and acetylcholine, which stimulate relaxation of the corpus cavernosum smooth muscle and produce erections.¹⁶ NO is an important regulator of cavernosal smooth muscle relaxation. NO also induces arterial dilation. NO diffuses to smooth muscle cells, where it augments the formation of cGMP, which acts as a second

messenger.¹⁷ At this point, the NO/cGMP/cGMP-dependent protein kinase I pathway serves as the principal regulatory basis for penile erection.⁷ This pathway offers multiple molecular sites for pharmacologic targeting, including catalytic enzymes, biochemical cofactors and products, and degradative enzymes. The enzyme PDE5 is a selective inactivator of cGMP in the cavernosal smooth muscle.¹⁸⁻²⁰ Most well known are the commercially available, orally effective PDE5-Is, such as sildenafil, vardenafil, and tadalafil.¹⁶ Similarly, sildenafil as a PDE5-I treats ED in the same manner.

Berner et al²¹ used a meta-analysis to show that sildenafil resulted in an effect of 9.65-point improvement. Tadalafil could be pooled into an effect of 8.52-point improvement, and vardenafil showed an effect of 7.50-point improvement. In our present studies, 200 mg sildenafil resulted in an effect of 8.62-point improvement, consistent with the study by Berner et al.²¹

Giuliano et al²² reported that the incidence of ED was approximately 61% in patients with hypertension. During the past 20 years, the relationship between ED and hypertension has increasingly become important owing to the increase in the number of patients with hypertension.²³ For hypertensive patients with ED, a previous meta-analysis²⁴ of 2427 patients demonstrated that vardenafil showed an average increase of 8.9 points in the IIEF-EF at week 12 compared with placebo. Our pooled results showed that sildenafil resulted in an average increase of 5.58-point improvement.

In the Massachusetts Male Aging Study, a landmark community-based survey of predominantly white men aged 40-69 years, the age-adjusted risk of developing ED for treated or untreated self-reported diabetic patients was 1.83 and was statistically significant.^{25,26} Approximately 50% of diabetic men develop ED at least once in the course of their disease. For the IIEF ED domain, Vardi and Nini²⁵ reported that sildenafil resulted in an effect of 7.83-point improvement. Tadalafil could be pooled into an effect of 3.39-point improvement, and vardenafil showed an effect of 3.93-point improvement. Our study indicated that sildenafil resulted in an effect of 4.06-point improvement.

In the present meta-analysis, the most common drug-related adverse events were flushing and headache. A recent meta-analysis²⁷ demonstrated that in short-term trials (<6 months), sildenafil-treated men had a greater risk of headache, flushing, dyspepsia, and visual disturbances compared with placebo-treated men. This indicated that sildenafil is comparable to sildenafil in drug-related adverse events.

Our meta-analysis also had several limitations. First, all included studies were of moderate quality²⁸ in this meta-analysis. This might not allow a reliable conclusion. Second, all participants came from Korea. Thus, more studies are needed from other countries and of other races to evaluate the effectiveness of sildenafil. Third, the dose of sildenafil ranged from 25 to 200 mg, and the optimal

dose needs to be explored further. Fourth, we lacked the data to perform subgroup analysis according to the duration and severity of ED.

CONCLUSIONS

The present meta-analysis suggested that tadalafil is an effective and well-tolerated therapy for ED. The findings of the present review highlight the need for more efficient performance of higher quality, large-sample, various-race, long-term, randomized controlled trials to verify the efficacy and safety of tadalafil.

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