Open Access

ORIGINAL ARTICLE

Avanafil for male erectile dysfunction: a systematic review and meta-analysis

Yuan-Shan Cui, Nan Li, Huan-Tao Zong, Hui-Lei Yan, Yong Zhang

Avanafil, a potent new selective phosphodiesterase type 5 (PDE5) inhibitor, has been developed for the treatment of erectile dysfunction (ED). We carried out a systematic review and meta-analysis to assess the efficacy and safety of this drug for the treatment of ED. A literature review was performed to identify all published randomized, double-blind, placebo-controlled trials of avanafil for the treatment of ED. The search included the following databases: MEDLINE, EMBASE and the Cochrane Controlled Trials Register. The reference lists of the retrieved studies were also investigated. Four publications, involving a total of 1381 patients, were used in the analysis, including four randomized controlled trials (RCTs) that compared avanafil with a placebo. Among the co-primary efficacy end points indicating that avanafil 100 mg was more effective than a placebo were successful vaginal penetration (SEP2) (the odds ratio (OR) =5.06, 95% confidence interval (CI) =3.29–7.78, $P < 0.00001$) and successful intercourse (SEP3) (OR = 3.99, 95% CI = 2.80–5.67, $P < 0.00001$). Men randomized to receive avanafil were less likely than those receiving the placebo to drop out due to an adverse event (AE) (OR = 1.48, 95% CI = 0.54–4.08, $P = 0.44$). Specific AEs with avanafil included headache and flushing, which were significantly less likely to occur with placebo. This meta-analysis indicates that avanafil 100 or 200 mg is an effective and well-tolerated treatment for ED. Compared with avanafil 100 mg, patients who take avanafil 200 mg are more likely to experience headaches.

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection for satisfactory sexual performance.[1] ED can have a neurogenic, psychogenic or endocrine basis; however, a common underlying cause is thought to be related to vascular abnormalities of the penile blood supply and erectile tissue. Studies indicate that ED is correlated with increased age, cardiovascular disease, diabetes, hypertension, smoking and depression.[2–4] ED must be considered a multidimensional disorder deriving from a general (or stepwise) perturbation of the organic (the body), relational (the couple) and intrapsychic (the mind) components of the erectile response.[5–7] Oral phosphodiesterase type 5 (PDE5) inhibitors are recommended as a first-line therapy for EDs of varying etiology and severity.[8,9] However, many patients are dissatisfied with the available therapies due to their high cost, adverse events (AEs) and perceived lack of efficacy.[10]

PDE5 plays an important role in regulating nitric oxide-mediated smooth muscle relaxation. PDE5 inhibitors are similar in structure to cGMP and competitively bind to PDE5. This binding inhibits the hydrolysis of cGMP, allowing for the accumulation of cGMP levels and leading to penile erection.[11] Avanafil, a PDE5 inhibitor, is highly selective for PDE5 and highly potent, with a 50% inhibitory concentration of 4.3–5.2 nmol l^{-1}.[12–14] It has higher selectivity (120-fold) against PDE6 than sildenafil (16-fold) and vardenafil (21-fold), as well as much higher selectivity (>10 000-fold) against PDE1 compared with sildenafil (380-fold) and vardenafil (1000-fold), which have recently been approved for the treatment of men with ED.[15]

The goal of the present study was to perform a meta-analysis evaluating the safety and efficacy of avanafil in the treatment of ED, which may resolve some of the current controversies over the use of the drug.

MATERIALS AND METHODS

Search strategy

MEDLINE (1966 to May 2013), EMBASE (1974 to May 2013) and the Cochrane Controlled Trials Register databases were searched to identify randomized controlled trials (RCTs) that referred to the impact of avanafil on the treatment of ED; we also searched the reference lists of the retrieved studies. The search terms used were as follows: 'Avanafil' and ('erectile dysfunction' or 'erectile and dysfunction') and ('randomized controlled trial' or 'random allocation' or 'random and allocation' or 'randomized and controlled and trial').

Inclusion criteria and trial selection

RCTs were included if they met the following criteria: (i) the study design included treatment with avanafil; (ii) the study provided accurate data that could be analyzed, including the total number of subjects and the values of each index and (iii) the full text of the study could be accessed. When the same study was published in various journals or in different years, the most recent publication

Department of Urology, Beijing Tian-Tan Hospital, Capital Medical University, Beijing, China.
Correspondence: Dr. Y Zhang (doctorzhy@126.com)

was used for the meta-analysis. If the same group of researchers studied a group of subjects with multiple experiments, then each study was included. A flow diagram of the study selection process is presented in **Figure 1**.

Quality assessment

The quality of the retrieved RCTs, which included assessment of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting of outcomes and other possible sources of bias, was assessed using the Jadad scale.[16] All of the identified RCTs were included in the meta-analysis, regardless of the quality score. The methodological quality of each study was assessed according to how patients were allocated to the arms of the study, the concealment of allocation procedures, blinding and data loss due to attrition. The studies were then classified qualitatively according to the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions v. 5.1.0.[17] Based on the quality assessment criteria, each study was rated and assigned to one of the three following quality categories: A, if all quality criteria were adequately met, the study was deemed to have a low risk of bias; B, if one or more of the quality criteria was only partially met or was unclear, the study was deemed to have a moderate risk of bias; or C, if one or more of the criteria was not met or not included, the study was deemed to have a high risk of bias. Differences were resolved by discussion among the authors.

Data extraction

The following information was collected for each study: (i) the name of the first author and the publication year, (ii) the study design and sample size, (iii) the therapy that the patients received, (iv) the country in which the study was conducted and (v) data including the successful vaginal penetration (SEP2), successful intercourse (SEP3), headache, flushing and discontinuations due to AEs.

Statistical analysis and meta-analysis

The meta-analysis of comparable data was carried out using RevMan v. 5.1.0 (Cochrane Collaboration, Oxford, UK).[17] Changes in the SEP2, SEP3, headache, flushing and discontinuations due to AEs were determined as differences between the baseline (study entry) and study completion. We estimated the relative risk for dichotomous outcomes and the standardized mean difference (SMD) for continuous outcomes pooled across studies by using the DerSimonian and Laird random-effects model.[18] We used a 95% confidence interval (CI). If the results of the analysis showed $P > 0.05$, we considered the studies homogeneous and chose a fixed-effect model for the meta-analysis. Otherwise, a random-effect model was used. We quantified the inconsistencies using the I^2 statistic, which indicates the proportion of heterogeneity across studies that is not due to chance, thereby describing the extent of true inconsistency in the results across trials.[18] $I^2 < 25\%$ reflects a small level of inconsistency and $I^2 > 50\%$ reflects significant inconsistency.

RESULTS

Characteristics of the individual studies

The database search found 51 articles that could have been included in our meta-analysis. Based on the inclusion and exclusion criteria, 36 articles were excluded after reading the titles and abstracts of the articles. Nine articles were not RCTs. Two articles lacked useful data. In all, four articles,[19–22] reporting data from a total of four RCTs that compared avanafil with placebo, were included in the analysis (**Figure 1**). The baseline characteristics of the studies included in our meta-analysis are listed in **Table 1**.

Quality of the individual studies

All four RCTs were double blinded and all described the randomization processes that they had used. All included a power calculation to determine the optimal sample size (**Table 2**). The level of quality of each identified study was A. The funnel plot provided a qualitative estimation of the publication bias of the studies and no evidence of bias was found (**Figure 2**).

Successful vaginal penetration

The four RCTs represented 889 participants (445 in the avanafil 100 mg group and 444 in the control group) (**Figure 3**). According to our analysis, no heterogeneity was found among the trials (**Figure 3**) and the effect size for the meta-analysis was denoted as the odds ratio (OR). The pooled estimate of OR was 5.06 and the 95% CI was 3.29–7.78 ($P < 0.00001$). This result suggests that avanafil showed statistically significant improvement in the SEP2 compared with placebo.

Successful intercourse

The four RCTs represented 889 participants (445 in the avanafil 100 mg group and 444 in the control group) (**Figure 3**). No heterogeneity was found among the trials (**Figure 3**). The pooled estimate of the OR was 3.99 and the 95% CI was 2.80–5.67 ($P < 0.00001$). This result suggests that avanafil showed statistically significantly greater improvement in the SEP3 compared with placebo.

Discontinuation due to adverse events

The four RCTs included data on discontinuation due to AEs and represented a cohort of 916 participants (457 in the avanafil 100 mg group and 459 in the control group) (**Figure 4**). The pooled estimate of the OR was 1.48 and the 95% CI was 0.54–4.08 ($P = 0.44$). These results suggest that avanafil and the placebo are similar in terms of the incidence of discontinuation due to AEs.

Treatment-emergent AEs (TEAEs)

Three RCTs, representing 778 participants (387 in the avanafil group and 391 in the control group), included TEAEs data (**Figure 4**). The pooled estimate of the OR was 1.97 and the 95% CI = 1.45–2.68, $P < 0.0001$. These results suggest that TEAEs with avanafil were significantly less likely to occur with the placebo.
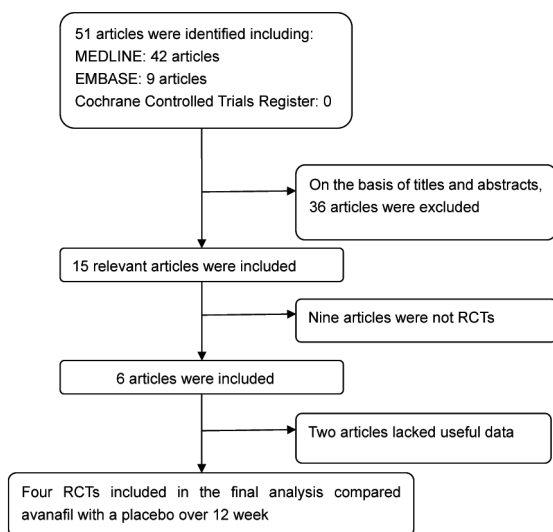
Figure 1: A flow diagram of the study selection process. RCT: randomized controlled trial.

### Table 1: Study and patient characteristics

Study	Therapy in experimental group	Therapy in control group	Country	Sample size (experimental)	Sample size (control)	Administration method	Duration of treatment (week)	Dosage	Inclusion population
Zhao *et al.*[19]	Avanafil	Placebo	Korea	71/69	68	Oral	12	100 mg/200 mg	Men >20 years with ED for ≥6 months
Goldstein *et al.*[20]	Avanafil	Placebo	US	162/162	161	Oral	12	100 mg/200 mg	Men ≥18 years with mild to severe ED for ≥6 months
Goldstein *et al.*[21]	Avanafil	Placebo	US	129/131	130	Oral	12	100 mg/200 mg	Men ≥18 years with mild to severe ED for ≥6 months and documented type 1 or 2 diabetes
Mulhall *et al.*[22]	Avanafil	Placebo	US	99/99	100	Oral	12	100 mg/200 mg	Men ≥8 years with ED for ≥6 months after bilateral nerve sparing retropubic radical prostatectomy

ED: Erectile dysfunction; US: United States

Table 2: Quality assessment of individual study

Study	Allocation sequence generation	Allocation concealment	Blinding	Loss to follow-up	Calculation of sample size	Statistical analysis	Intention-to-treat analysis	Level of quality
Zhao *et al.*[19]	A	A	A	8	Yes	Analysis of covariance	Yes	A
Goldstein *et al.*[20]	A	A	A	17	Yes	Analysis of covariance	Yes	A
Goldstein *et al.*[21]	A	A	A	11	Yes	Analysis of covariance	Yes	A
Mulhall *et al.*[22]	A	A	A	12	Yes	Analysis of covariance	Yes	A

A, all quality criteria met (adequate): low risk of bias; B, one or more of the quality criteria only partly met (unclear): moderate risk of bias; C, one or more criteria not met (inadequate or not used): high risk of bias
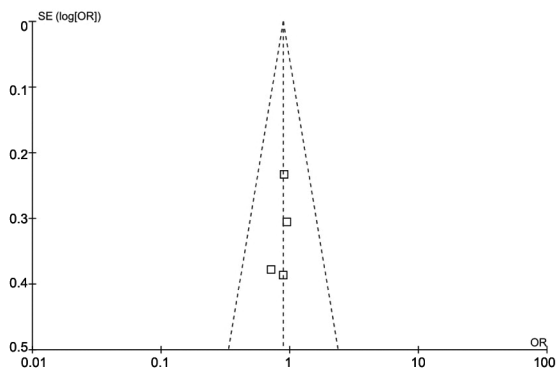
Figure 2: Funnel plot of the studies represented in our meta-analysis. OR: odds ratio; SE: standard error.

Headache and flushing

Four RCTs included the headache data, representing a cohort of 916 participants (457 in the avanafil 100 mg group and 459 in the control group) (**Figure 4**). The pooled estimate of the OR was 5.48 and the 95% CI was 2.18–13.78 ($P = 0.0003$). The four RCTs also included the flushing data, representing a cohort of 916 participants (457 in the avanafil 100 mg group and 459 in the control group) (**Figure 4**). The pooled estimate of the OR was 8.12 and the 95% CI was 2.62–25.13 ($P = 0.0003$). These results suggest that the specific AEs with avanafil, including headache and flushing, were significantly less likely to occur with the placebo.

Avanafil 100 mg versus avanafil 200 mg

The four RCTs with SEP2 and SEP3 data included 889 participants (445 in the avanafil 100 mg group and 444 in the avanafil 200 mg group) (**Figure 5**). For the avanafil 100 mg group, the OR was 0.88, with a 95% CI of 0.66–1.19 ($P = 0.42$). For the avanafil 200 mg group, the OR was 0.87, with a 95% CI of 0.66–1.16 ($P = 0.34$). These results suggest that

avanafil 100 and 200 mg are similarly effective for patients with ED. Four RCTs included discontinuation due to AEs, headache and flushing data and represented 918 participants (447 in the avanafil 100 mg group and 461 in the avanafil 200 mg group) (**Figure 5**). These results suggest that the safety profile of avanafil 100 mg appears to be comparable with that of avanafil 200 mg (OR = 1.01, 95% CI 0.41–2.50, $P = 0.99$) (**Figure 5**), while patients who took avanafil 200 mg were more likely to experience headaches (OR = 0.55, 95% CI 0.34–0.89, $P = 0.01$) (**Figure 5**).

Sensitivity analysis

Sensitivity analysis was performed by dividing the included studies into a US and an Asian group. Our analysis indicated that avanafil showed statistically significant improvement in the SEP2 (OR = 6.67, 95% CI 4.01 to 11.12, $P<0.00001$ and OR = 2.02, 95% CI 0.85 to 4.77, $P = 0.01$) and SEP 3 (OR = 4.15, 95% CI 2.78 to 6.21, $P<0.00001$ and OR = 3.44, 95% CI 1.66 to 7.13, $P = 0.0009$) groups in both the US and the Asian group. No differences were found between the avanafil 100 mg and avanafil 200 mg groups regarding changes in the SEP2 (OR = 0.88, 95% CI 0.64–1.22, $P = 0.45$ and OR = 0.89, 95% CI 0.42–1.90, $P = 0.76$, respectively) or SEP3 (OR = 0.86, 95% CI 0.63–1.17, $P = 0.34$ and OR = 0.94, 95% CI 0.47–1.85, $P = 0.85$, respectively) in either the US or the Asian group.

DISCUSSION

ED affects 30 million men in the United States and 150 million worldwide. This number is expected to increase as the population ages.[23] ED occurs more often in males with diabetes, heart disease, previous radical prostatectomy and neurologic conditions. ED is also associated with cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, chronic kidney disease and obesity.[24] The PDE5 inhibitors have been shown to restore penile blood flow and erections in response to sexual stimulation.[25] Despite these options, many men suffering from ED fail to respond clinically. Most of these men are patients with severe ED involving diabetes mellitus, severe vascular insufficiency or postprostatectomy complications. Newer medications
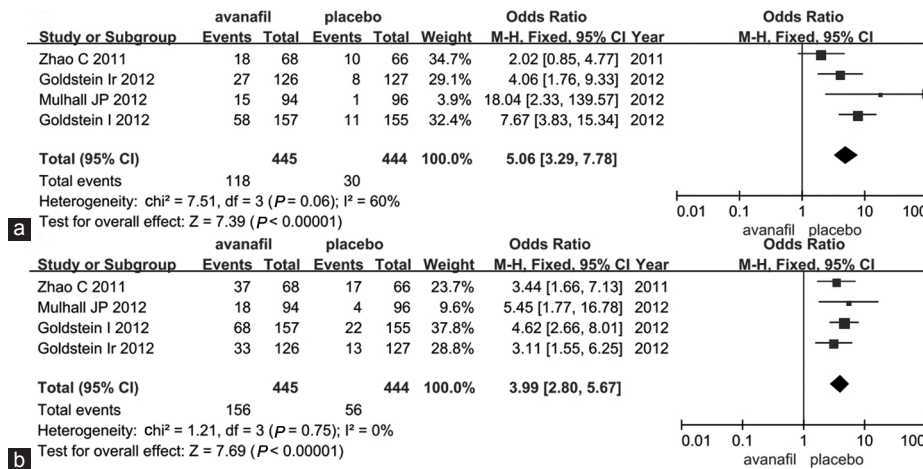
Figure 3: Forest plots showing changes in (**a**) successful vaginal penetration and (**b**) successful intercourse. CI: confidence interval; MH: Mantel–Haenszel.
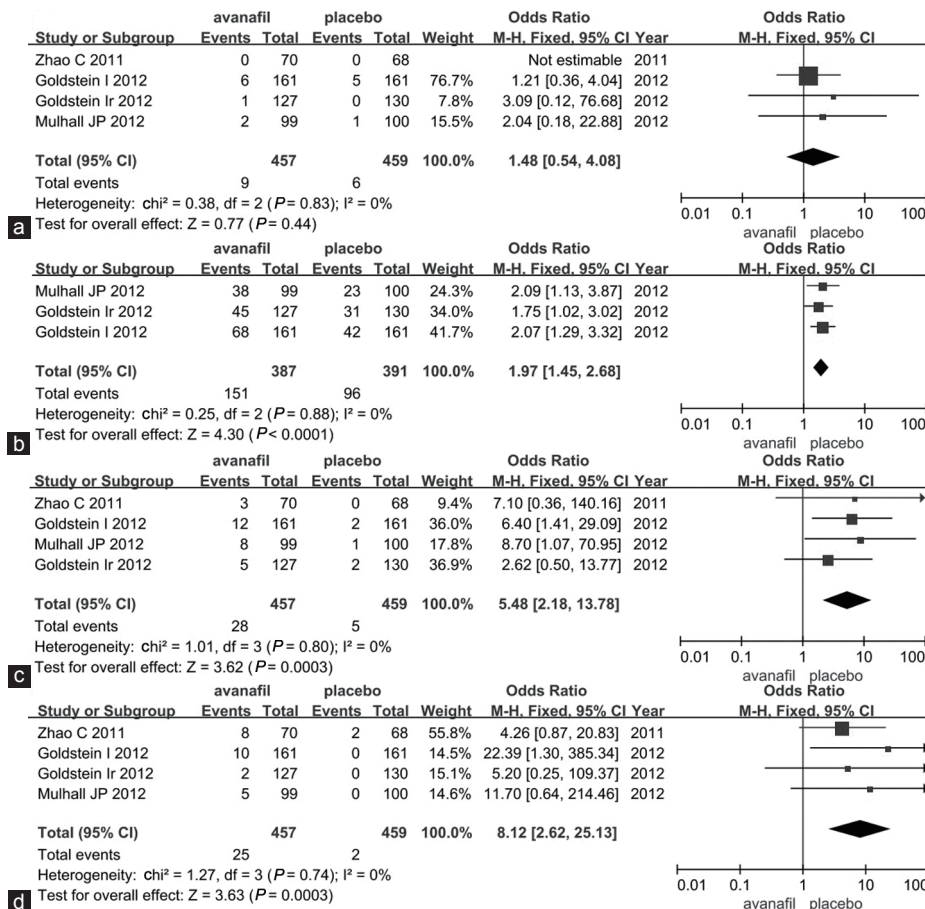

Figure 4: Forest plots showing changes in (**a**) discontinuation due to adverse events, (**b**) treatment-emergent adverse events, (**c**) headache and (**d**) flushing. CI: confidence interval; MH: Mantel–Haenszel.

in the PDE5 inhibitor class that have greater efficacy and lower adverse reaction profiles are being studied.[23] Avanafil is a novel PDE5 inhibitor that has been shown to have a greater selectivity for PDE5 and a higher selectivity against PDE1 and PDE6.[19]

This systematic review and quantitative meta-analysis summarizes the evidence from randomized controlled clinical trials regarding the efficacy and safety of avanafil for the treatment of ED. Overall, compared with men receiving placebos, those allocated to the avanafil

group had a higher percentage of SEP2 and were more likely to have SEP3. Compared with the meta-analysis of PDE5 inhibitors,[26] avanafil (2.78-fold of placebo) performed significantly better than sildenafil (1.94-fold of placebo), vardenafil (1.94-fold of placebo) or tadalafil (2.09-fold of placebo) with regard to SEP3 improvement. Moreover, treatment with 100 mg avanafil was associated with significant improvements in the International Index of Erectile Function-erectile function (IIEF-EF) domain score compared with

placebo in the primary efficacy end points across all included RCTs. In addition, significant improvements in key secondary efficacy end points of each domain of IIEF (orgasmic function, intercourse satisfaction, sexual desire and overall satisfaction) were observed for the avanafil treatment group compared with placebo.

Safety data from the trials in this meta-analysis suggest that avanafil administration was generally well-tolerated. Although TEAEs were significantly more frequent with avanafil use than with placebo, they were mostly mild or moderate in severity and discontinuation due to AEs occurred no more frequently with avanafil use than with placebo. The most commonly reported TEAEs were headache and flushing, but they were all well-tolerated. All of the included RCTs indicated no clinically significant changes in laboratory tests, electrocardiograms or blood pressure in the avanafil groups.

All four of the included RCTs showed that avanafil 100 and 200 mg are similarly effective for a large proportion of patients with ED (**Figure 5**). The safety profile of avanafil 100 mg appears to be comparable with that of avanafil 200 mg, with similar side effects being present. Patients who took avanafil 200 mg were more likely to have a headache (**Figure 5**). Men were instructed to take the study drug approximately 30 min before the initiation of sexual activity in all of the included RCTs. Combined with the effective results, the onset of action of avanafil appears to be shorter than that of sildenafil. The unique clinical properties (higher selectivity and faster onset) of avanafil will provide a welcome addition to current ED management strategies. Compared with the meta-analysis of PDE5 inhibitors,[26]

the incidence of headache and flushing while taking avanafil (6.1% *vs* 1.1% and 5.5% *vs* 0.4%, respectively) was much lower than with sildenafil (14.2% *vs* 4.3% and 11.4% *vs* 1.6%), vardenafil (10.6% *vs* 2.5% and 10.0% *vs* 0.8%) and tadalafil (11.0% *vs* 3.0% and 4.0% *vs* 1.1%). Only two cases of vision abnormality were discovered in the four included RCTs. The rate was much lower than that for sildenafil.[27] These observed AE data for avanafil might be correlated with its favorable pharmacokinetic profile and greater selectivity for PDE5. Avanafil has a higher selectivity (120-fold) against PDE6 than sildenafil (16-fold) and vardenafil (21-fold), as well as a much higher selectivity (>10 000-fold) against PDE1 than sildenafil (380-fold) or vardenafil (1000-fold). Avanafil does not inhibit PDE11. Color vision disturbances are believed to be attributable to the nonspecific inhibition of certain PDE inhibitors, specifically PDE6.[28]

The studies included in the present meta-analysis all derived their data from randomized, double-blind, placebo-controlled trials. According to the quality assessment scale that we developed, the quality of the individual studies in the meta-analysis was conforming. The results of this analysis have great importance not only from the scientific standpoint, but also from that of everyday clinical practice. However, few studies were included in this analysis and the long-term safety, efficacy and persistence of avanafil cannot be extrapolated here. In addition, the data from unpublished studies were not included in the analysis and these factors may have resulted in a bias. Additional high-quality trials with larger samples are proposed to learn more about the efficacy and safety of the therapies for ED.
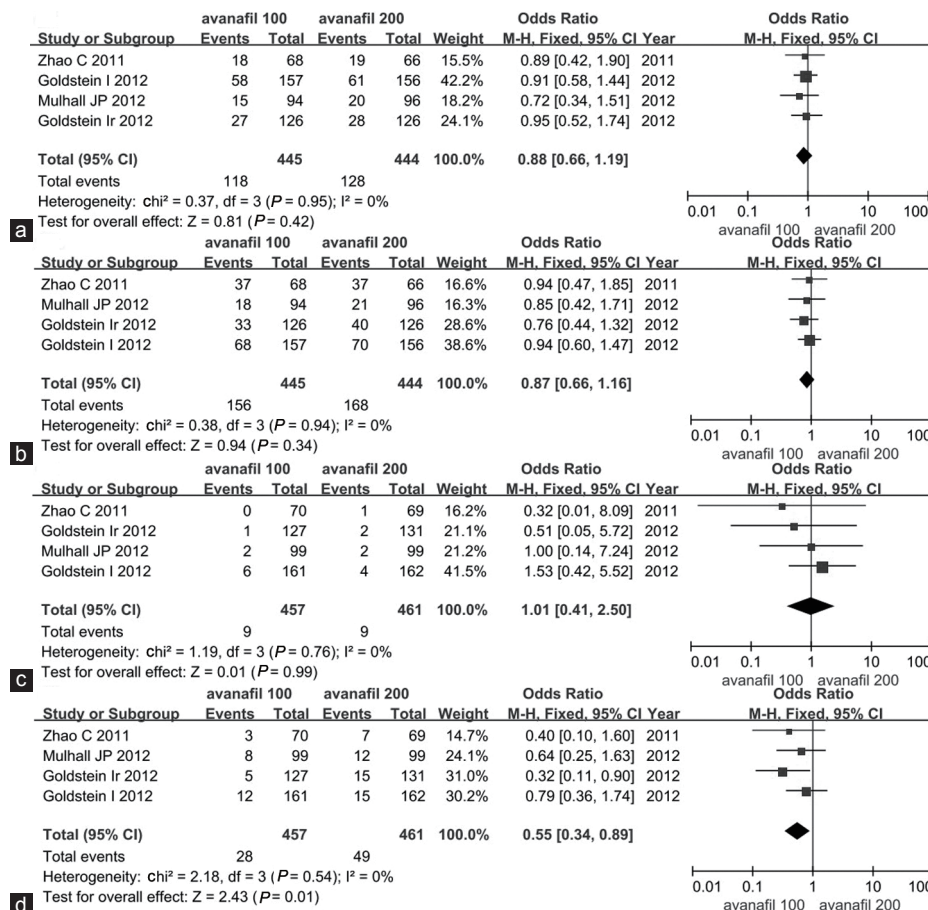
Figure 5: Forest plots showing changes in (**a**) successful vaginal penetration, (**b**) successful intercourse, (**c**) discontinuation due to adverse events and (**d**) headache. CI: confidence interval; MH: Mantel–Haenszel.

CONCLUSION

This meta-analysis indicates that avanafil 100 or 200 mg is an effective and well-tolerated treatment for ED. However, compared with avanafil 100 mg, patients who take avanafil 200 mg are more likely to experience headaches.

AUTHOR CONTRIBUTIONS

YSC and YZ conceived of the study, participated in its design and coordinated and drafted the manuscript. YSC, YZ, NL, HTZ and HLY collected the data. YSC, YZ and NL performed the statistical analyses. YSC, YZ and HTZ participated in critical revision of the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

REFERENCES

1 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, *et al*. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N Engl J Med* 1998; 338: 1397–404.
2 Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, *et al*. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts Male Aging Study. *J Urol* 2000; 163: 460–3.
3 Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. *Am J Med* 2007; 120: 151–7.
4 Wyllie MG. The underlying pathophysiology and causes of erectile dysfunction. *Clin Cornerstone* 2005; 7: 19–27.
5 Corona G, Petrone L, Mannucci E, Magini A, Lotti F, *et al*. Assessment of the relational factor in male patients consulting for sexual dysfunction: the concept of couple sexual dysfunction. *J Androl* 2006; 27: 795–801.
6 Lewis RW, Fugl-Meyer KS, Corona G, Hayes RD, Laumann EO, *et al*. Definitions/epidemiology/risk factors for sexual dysfunction. *J Sex Med* 2010; 7: 1598–607.
7 Corona G, Mondaini N, Ungar A, Razzoli E, Rossi A, *et al*. Phosphodiesterase type 5 (PDE5) inhibitors in erectile dysfunction: the proper drug for the proper patient. *J Sex Med* 2011; 8: 3418–32.
8 Montague DK, Jarow JP, Broderick GA, Dmochowski RR, Heaton JP, *et al*. Chapter 1: the management of erectile dysfunction: an AUA update. *J Urol* 2005; 174: 230–9.
9 Wespes E, Amar E, Hatzichristou D, Hatzimouratidis K, Montorsi F, *et al*. EAU Guidelines on erectile dysfunction: an update. *Eur Urol* 2006; 49: 806–15.
10 Madduri SD. After two years, did Viagra live up to its expectations? *Mo Med* 2001; 98: 243–5.
11 Palit V, Eardley I. An update on new oral PDE5 inhibitors for the treatment of erectile dysfunction. *Nat Rev Urol* 2010; 7: 603–9.
12 Kotera J, Mochida H, Inoue H, Noto T, Fujishige K, *et al*. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. *J Urol* 2012; 188: 668.
13 Wang R, Burnett AL, Heller WH, Omori K, Kotera J, *et al*. Selectivity of avanafil, a PDE5 inhibitor for the treatment of erectile dysfunction: implications for clinical safety and improved tolerability. *J Sex Med* 2012; 9: 2122–9.
14 Allison M, Grant T, Obaidi M, Marenco T, Yee S, *et al*. Pharmacokinetics of avanafil, a novel, rapidly absorbed, selective PDE5 inhibitor for the treatment of mild to severe erectile dysfunction. *J Sex Med* 2011; suppl 8: S466.
15 STENDRA (avanafil) tablets prescribing information. Mountain View, California: VIVUS, Inc 2012.
16 Jadad AR. Randomised controlled trials. London: BMJ Publishing Group1998.
17 Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, v. 5.1 [updated March 2011]. Cochrane Collaboration Web site. Available from: http://www.cochrane-handbook.org.
18 DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88.
19 Zhao C, Kim SW, Yang DY, Kim JJ, Park NC, *et al*. Efficacy and safety of avanafil for treating erectile dysfunction: results of a multicentre, randomized, double-blind, placebo-controlled trial. *BJU Int* 2012; 110: 1801–6.
20 Goldstein I, McCullough AR, Jones LA, Hellstrom WJ, Bowden H, *et al*. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med* 2012; 9: 1122–33.
21 Goldstein I, Jones LA, Belkoff LH, Karlin GS, Bowden CH, *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: 843–52.
22 Mulhall JP, Burnett AL, Wang R, McVary KT, Moul JW, *et al*. A Phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. *J Urol* 2012; 189: 2229–36.
23 Limin M, Johnsen N, Hellstrom WJ. Avanafil, a new rapid-onset phosphodiesterase 5 inhibitor for the treatment of erectile dysfunction. *Expert Opin Investig Drugs* 2010; 19: 1427–37.
24 Alwaal A, Al-Mannie R, Carrier S. Future prospects in the treatment of erectile dysfunction: focus on avanafil. *Drug Des Devel Ther* 2011; 5: 435–43.
25 Hellstrom WJ, Freier MT, Serefoglu EC, Lewis RW, DiDonato K, *et al*. A phase II, single-blind, randomized, crossover evaluation of the safety and efficacy of avanafil using visual sexual stimulation in patients with mild to moderate erectile dysfunction. *BJU Int* 2013; 111: 137–47.
26 Tsertsvadze A, Fink HA, Yazdi F, MacDonald R, Bella AJ, *et al*. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. *Ann Intern Med* 2009; 151: 650-61.
27 Padmanathan H, Eardley I, Kloner RA, Laties AM, Montorsi F. A 4-year update on the safety of sildenafil citrate (Viagra). *Urology* 2002; 60: 67–90.
28 Hatzimouratidis K, Hatzichristou DG. A comparative review of the options for treatment of erectile dysfunction: which treatment for which patient? Drugs 2005; 65: 1621–50.