Meta-Analysis of the Long-Term Efficacy and Tolerance of Tadalafil Daily Compared With Tadalafil On-Demand in Treating Men With Erectile Dysfunction

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ABSTRACT

Background: Erectile dysfunction (ED) is highly prevalent in aging men. Tadalafil daily and on-demand are widely used for the treatment of ED.

Aim: We performed a meta-analysis to evaluate the efficacy and safety of tadalafil daily compared with tadalafil on-demand in treating men with ED after at least 24 weeks of long-term treatment.

Methods: Randomized controlled trials of tadalafil daily vs on-demand in treating men with ED were searched using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register. Systematic review was carried out using the Preferred Reporting Items for Systematic Reviews and Meta-analyses. The data was calculated by RevMan version 5.3.0. The references of related articles were also searched.

Outcomes: International Index of Erectile Function-Erectile Function domain, sexual encounter profile question 2 (SEP2), SEP question 3 (SEP3), any treatment-emergent adverse event (AE), discontinuation due to AEs, myalgia, back pain, headache, dyspepsia, and nasopharyngitis.

Results: 4 articles, including 1,035 participants were studied. The analysis found that tadalafil daily had a greater improvement than tadalafil on-demand in terms of International Index of Erectile Function-Erectile Function (mean difference (MD) 1.24; 95% CI 0.03−2.44; $P = .04$), SEP2 (MD 10.08; 95% CI 9.15−11.01; $P < .00001$) and SEP3 (MD 8.19; 95% CI 2.09−14.29; $P = .009$) in treating ED after at least 24 weeks treatment cycle. For safety, tadalafil on-demand had a higher incidence of any treatment-emergent AE (odds ratio 0.73; 95% CI 0.56−0.96; $P = .02$) compared with tadalafil daily, but for other aspects, including discontinuation due to AEs, myalgia, back pain, headache, dyspepsia, and nasopharyngitis, there were no significant difference between the 2 treatments.

Clinical Implications: Tadalafil daily may offer a better effect for ED than on-demand for long-term treatment.

Strengths and Limitations: From the perspective of evidence-based medicine, we evaluated the efficacy and safety of tadalafil daily compared with tadalafil on-demand in treating men with ED after a long-term treatment. The quality of these studies included is flawed, primarily in difference in tadalafil doses and severity of the ED.

Conclusion: Tadalafil daily provides a preferable therapeutic effect for ED with a lower incidence of treatment-emergent side effects relative to tadalafil on-demand after at least 24 weeks of long-term treatment. **Zhou Z, Chen H, Wu J, et al. Meta-Analysis of the Long-Term Efficacy and Tolerance of Tadalafil Daily Compared With Tadalafil On-Demand in Treating Men With Erectile Dysfunction. J Sex Med 2019;7:282−291.**

INTRODUCTION

Erectile dysfunction (ED) is an important male health condition that involves negative impacts for self-confidence and quality of life (QOL).[1,2] It is a problem getting or keeping an erection hard enough for satisfactory sexual performance, which increases with age from 35% of men aged 60 to 50% of men older than 70.[3–5]

Tadalafil, as a selective phosphodiesterase type 5 (PDE5) inhibitor, can be rapidly absorbed with a half-life of 17.5 hours.[6] Some clinical trials followed up for 12 weeks have showed that men taking tadalafil had a remarkable improvement in the International Index of Erectile Function-Erectile Function (IIEF-EF) domain score with a successful completion of intercourse attempts and a higher rate of improved erections.[7,8] Recently, there is still some debate about the way tadalafil is administered. A study found that once-a-day tadalafil did not provide a clinically significant increase in IIEF-EF scores compared with on-demand tadalafil after 12 weeks of short-term treatment.[9] However, there is no evidence-based medicine to prove the advantages and disadvantages between tadalafil daily and tadalafil on-demand after long-term treatment.

We performed a meta-analysis to evaluate the efficacy and safety of tadalafil daily compared with tadalafil on-demand in treating men with ED after at least 24 weeks of long-term treatment.

MATERIALS AND METHODS

Study Protocol

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to systematic review of randomized controlled trials (RCTs).[10]

Information Sources and Literature Search

We searched MEDLINE (1996 to December 2018), EMBASE (1999 to December 2018), and the Cochrane Controlled Trials Register to investigate tadalafil daily vs tadalafil on-demand in treating men with ED after at least 24 weeks of long-term treatment. The search terms were as follows: "tadalafil, erectile dysfunction, and RCT." All articles were browsed and read independently by 2 authors, and if there was any controversy, it was referred to the third person for assessment. The study only included published literature with no restriction on language or region. If the study was a review or summary presented at the meeting, it would be excluded. If necessary, authors were contacted to offer further information from their study. The references of related articles were also searched.

Inclusion Criteria and Trial Selection

Inclusion criteria was described as follows: (1) tadalafil daily vs tadalafil on-demand in treating men with ED was involved; (2)

full-text content and related data can be obtained; (3) articles offered accurate data mainly including the number of subjects and the valuable results of indicators; (4) trials were RCTs; (5) the duration of treatment was at least 24 weeks. Additionally, the most recently published study was included in the meta-analysis if an identical study was published in distinct journals or at a different time point. When the same group of researchers investigated a certain subject group in multiple experiments, each study was included. The PRISMA diagram of selection is shown in Figure 1.

Quality Assessment Methods

The Jadad Scale was used to evaluate the quality of each RCT.[11] Additionally, some methods of assessment were used to analyze the quality of the individual studies, including method of patient allocation, concealment of allocation, blinding method, and number lost to follow-up. Individual studies were graded in line with the principles that were derived from the *Cochrane Handbook for Systematic Reviews of Interventions v5.10.*[12] Every study was classified based on quality assessment criteria: (A) satisfying almost all of the quality criteria, the study would be considered to have a low probability of bias; (B) ambiguous about one or more quality criteria, the study would be considered to have a secondary probability of bias; or (C) satisfying bare quality criteria, the study was considered to have a high probability of bias. All authors participated in the assessment of retrieved study, eventually everyone agree with these results. All reviewers independently assessed whether the study fit into the criteria, and then extracted data from each study. Differences regarding the quality assessment were resolved by discussion among the reviewers.

Data Extraction

The usable data was extracted from each study: (a) published time; (b) the first author's name; (c) country of study; (d) the type of design; (e) the patient's received therapy; (d) capacity of sample;
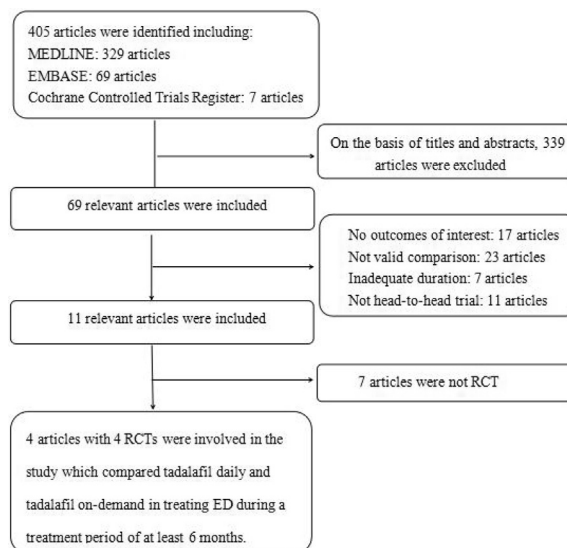

Figure 1. Flowchart of the study selection process. ED, erectile dysfunction; RCT, randomized controlled trial.

Table 1. The details of individual study

Study	Country	Study design	Therapy in experimental group	Therapy in control group	Sample size Experimental	Control	Method	Follow-up period (wk)	Dosage	Main inclusion criteria	Main exclusion criteria
McMahon et al[14] (2005)	Australia	RCT	Tadalafil daily	Tadalafil on-demand	75	70	Oral	26	Tadalafil (20 mg) on-demand or tadalafil (10 mg) daily	Men 18 years of age or older in a stable heterosexual relationship for >3 mo or longer history of ED	Men with anatomic abnormalities of the penis that could impair EF and any myocardial infarction or life-threatening cardiac arrhythmia within the previous 6 mo
Jamshidian et al[15] (2012)	Iran	RCT	Tadalafil daily	Tadalafil on-demand	50	50	Oral	24	Tadalafil (10 mg) on-demand or tadalafil (10 mg) daily	Men ≥18 years were involved in study if they had a ≥3 mo history of ED	Men with hypoactive sexual desire, treated or untreated hypogonadism, a history of radical prostatectomy, ED after spinal cord injury, severe chronic liver disease, or severe chronic renal failure
Montorsi et al[16] (2013)	9 European countries and Canada	RCT	Tadalafil daily	Tadalafil on-demand	139	142	Oral	36	Tadalafil (20 mg) on-demand or tadalafil (5 mg) daily	Men with newly diagnosed PCa claim to have unimpaired EF but have IIEF-EF scores of 22−25 (mild ED)	Men treated with PDE5 inhibitors, presence of penile implant, or clinically significant penile deformity
Buvat et al[17] (2013)	8 European countries	RCT	Tadalafil daily	Tadalafil on-demand	257	252	Oral	24	Tadalafil (10 mg) on-demand or tadalafil (5 mg) daily	Men (≥18 years) were eligible to participate if they had ≥3-mo history of ED	Previous treatment with or contraindications for PDE-5 inhibitors, ED caused by other sexual or endocrine disorders, history of radical prostatectomy, or other pelvic surgery resulting in ED

ED = erectile dysfunction; EF = erectile function; IIEF-EF = International Index of Erectile Function-Erectile Function domain; RCT = randomized controlled trial; PDE-5 = phosphodiesterase type 5; PCa = prostate cancer.

Table 2. Quality assessment of individual study.

Study	Allocation sequence generation	Allocation concealment	Blinding	Lost to follow-up	Calculation of sample size	Statistical analysis	Level of quality	ITT analysis
McMahon et al[14] (2005)	A	A	B	9	No	ANOVA	A	No
Jamshidian et al[15] (2012)	A	A	A	0	Yes	ANOVA	A	Yes
Montorsi et al[16] (2013)	A	A	A	14	Yes	Cochran-Mantel-Haenszel test; Fisher's exact test; ANOVA	A	Yes
Buvat et al. (2013)	A	A	A	3	Yes	Cochran-Mantel-Haenszel test; ANOVA	A	Yes

A, almost all quality criteria met: low risk of bias; B, one or more quality criteria met : moderate risk of bias; C, one or more criteria not met: high risk of bias. ANOVA = analysis of variance; ITT = intention-to-treat.

(e) drug management; (f) treatment period; (g) drug dose; (h) data on IIEF-EF, sexual encounter profile question 2 (SEP2), sexual encounter profile question 3 (SEP3), any treatment-emergent adverse event (AE), discontinuation due to AEs, myalgia, back pain, headache, dyspepsia, and nasopharyngitis. These results had clinical significance because they made a measurable impact on patients. No ethical approval was required for our study.

The IIEF questionnaire comprises 15 questions aimed at assessing sexual function, and is divided into 5 domains. The most often quoted domain is the IIEF-EF domain, where EF refers to erectile function. Within the IIEF-EF domain, there are 6 questions, and you gain up to 5 points per question. The questions refer only to the previous 4 weeks and ask the following: (i) How often during sexual activity did you gain an erection? (ii) How often were erections hard enough for penetration? (iii) When you attempted penetration, how often did you succeed? (iv) How well did you maintain the erection after penetration? (v) How well did you maintain the erection to orgasm? (xv) How high was your confidence that you could get and keep an erection?

Patients' responses to question 2 of the SEP Diary: Were you able to insert your penis into your partner's vagina? Question 3 of the SEP Diary: Did your erection last long enough for you to have successful intercourse?

The primary outcome of our study was IIEF-EF. The IIEF-EF scores were theoretically categorized into the following ED severity categories: severe (0−10), moderate (11−16), mild (17−25), and normal (26−30). The lower scores of IIEF indicated more severe symptoms. Secondary outcomes, including SEP2 and SEP3, were reported consistently enough among studies to allow for analysis of data. In addition, we also analyzed the number of any treatment-emergent AE, discontinuation due to AEs, myalgia, back pain, headache, dyspepsia, and nasopharyngitis between the 2 groups.

Statistical Analyses and Meta-Analysis

RevMan version 5.3.0 (Cochrane Collaboration, Oxford, UK[13]) was used to the analysis of data. The Fixed or random-effects models were applied to assess each indicator. Mean difference (MD) was used to explain continuous data and odds ratio (OR) for dichotomous results with corresponding 95% CI.[13] If the result showed P value > .05, the study was homogeneous, and fixed-effect model was used to the evaluation of data. The study analyzed inconsistency by using I^2 statistic that reflected the proportion of heterogeneity in the study. A random-effect model would be used for the result where I^2 value is > 50%. If the P value was < .05, the result was considered statistically significant.

RESULTS

Study Selection Process, Search Results, and Characteristics of the Trials

Our search found 405 articles in the database. Scrutinizing all abstracts and titles, we excluded 339 articles. For the
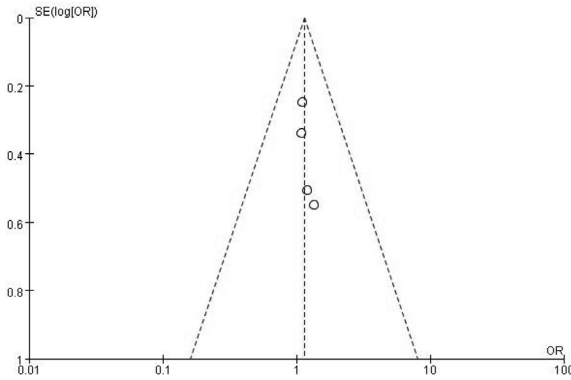
Figure 2. Funnel plot of the studies included in our meta-analysis. OR, odds ratio; SE, standard error.

remaining 69 articles, 58 articles were excluded because of lack of available data, 7 articles were excluded because they were not RCTs (details in Figure 1). Finally, 4 articles containing 4 RCTs[14−17] were used to evaluate the efficacy and safety of tadalafil daily compared with tadalafil on-demand in treating men with ED after at least 24 weeks of long-term treatment. The details of 4 articles are listed in Table 1. Patients with ED included in each study showed similar evaluation index.

Risk of Bias in Studies

All studies included in the analysis were random control studies and did not specify a random protocol. Three

studies[15−17] had an appropriate calculation of sample size to analyze. Three studies[15−17] showed intention-to-treat analysis. However, in McMahon et al,[14] the specific method of blind was not explicitly explained with Jadad scores rating B. In addition, the difference in tadalafil doses used for the treatments may affect our final results. All of the included studies demonstrated high quality with Jadad scores rating A (Table 2). The funnel plot was highly symmetrical and 4 circles were contained in the large triangle, and no evidence of bias was found (Figure 2).

Efficacy

IIEF-EF

4 RCTs with an amount of 1,035 patients (521 in the tadalafil daily group and 514 in the tadalafil on-demand group) were used to analyze the change of IIEF-EF. The forest plot demonstrated that the tadalafil daily group had a greater increase of IIEF-EF score (MD = 1.24; 95% CI = 0.03−2.44; P = .04; Figure 3A) compared with the tadalafil on-demand group. This result suggested that tadalafil daily can significantly alleviate the subjective symptoms of patients relative to tadalafil on-demand.

The higher heterogeneity was found among studies in the forest plots (P < .00001; I^2 = 99%). We did a subgroup analysis by the difference between the doses used for the treatments and no significant differences were found among subgroups (P = .27; I^2 = 23.5%; Figure 4).
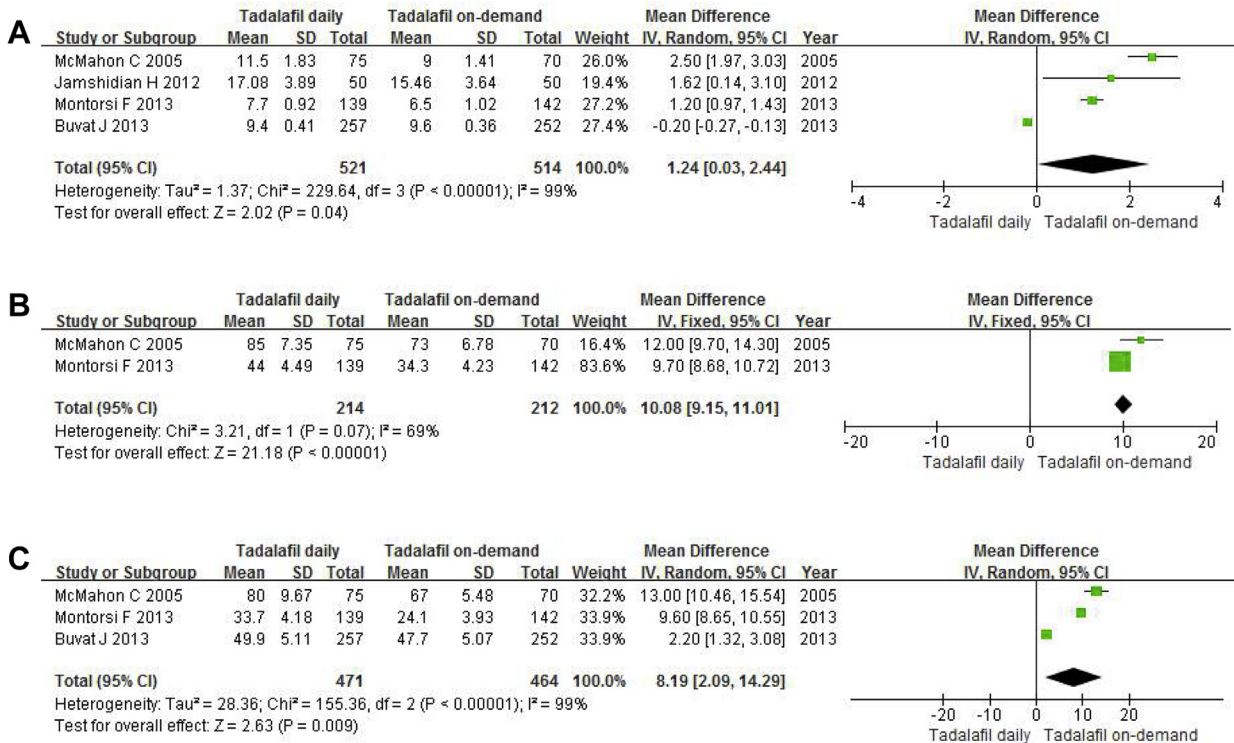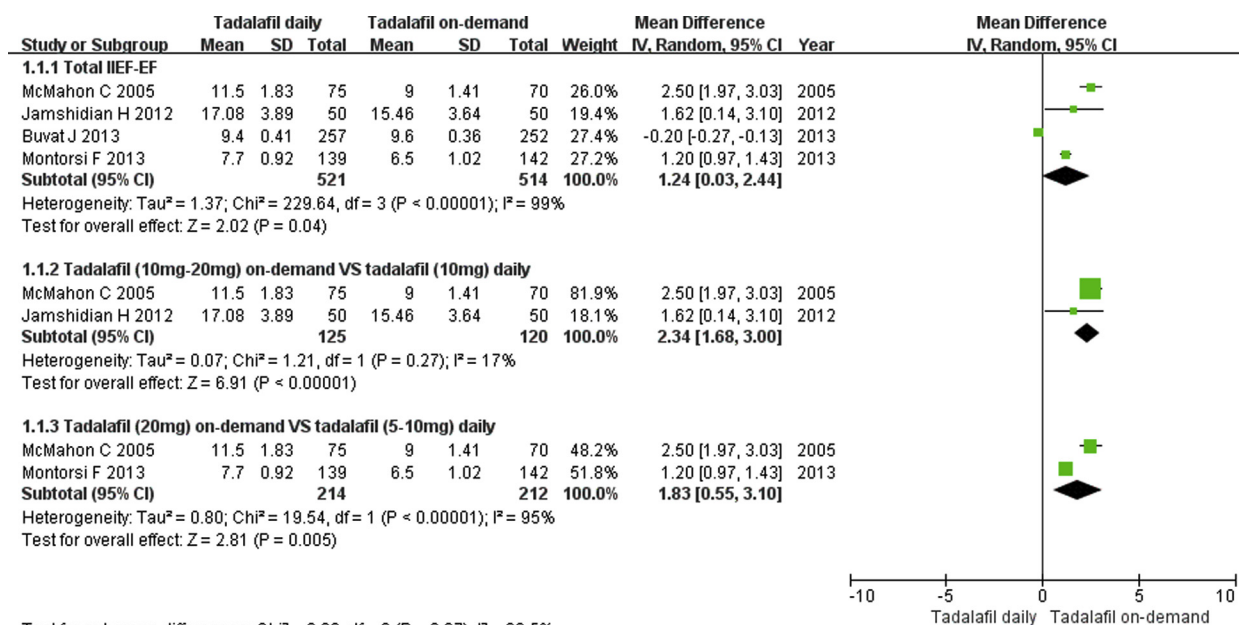

Figure 3. Forest plots showing change in (A) International Index of Erectile Function-Erectile Function domain, (B) Sexual Encounter Profile Question 2, and (C) Sexual Encounter Profile Question 3. df, degrees of freedom; IV, inverse variance.

Figure 4. Subgroup analysis of International Index of Erectile Function-Erectile Function (IIEF-EF) by the difference between the doses used for the treatments. df, degrees of freedom; IV, inverse variance.

SEP2

2 RCTs with an amount of 426 patients (214 in the tadalafil daily group and 212 in the tadalafil on-demand group) included data on the change of SEP2. The tadalafil daily group was significantly superior to the tadalafil on-demand group in increasing the score of SEP2 (MD = 10.08; 95% CI = 9.15−11.01; $P < .00001$; Figure 3B). This result suggested that tadalafil daily could significantly improve the subjective symptoms of patients compared with tadalafil on-demand.

SEP3

3 RCTs enrolling 935 patients (471 in the tadalafil daily group and 464 in the tadalafil on-demand group) contained data on the

SEP3. The forest plots showed an MD of 8.19 and 95% CI of 2.09−14.29 ($P = .009$; Figure 3C). We found that there was statistical significance between the tadalafil daily group and tadalafil on-demand group for the improvement of SEP3.

Safety

Any treatment-emergent AE

3 RCTs with a sample of 935 patients (471 in the tadalafil daily group and 464 in the tadalafil on-demand group) evaluated the incidence of any treatment-emergent AE. The study showed that tadalafil daily had a lower incidence of any treatment-emergent AE compared with tadalafil on-demand (OR = 0.73; 95% CI = 0.56−0.96; $P = .02$; Figure 5A).
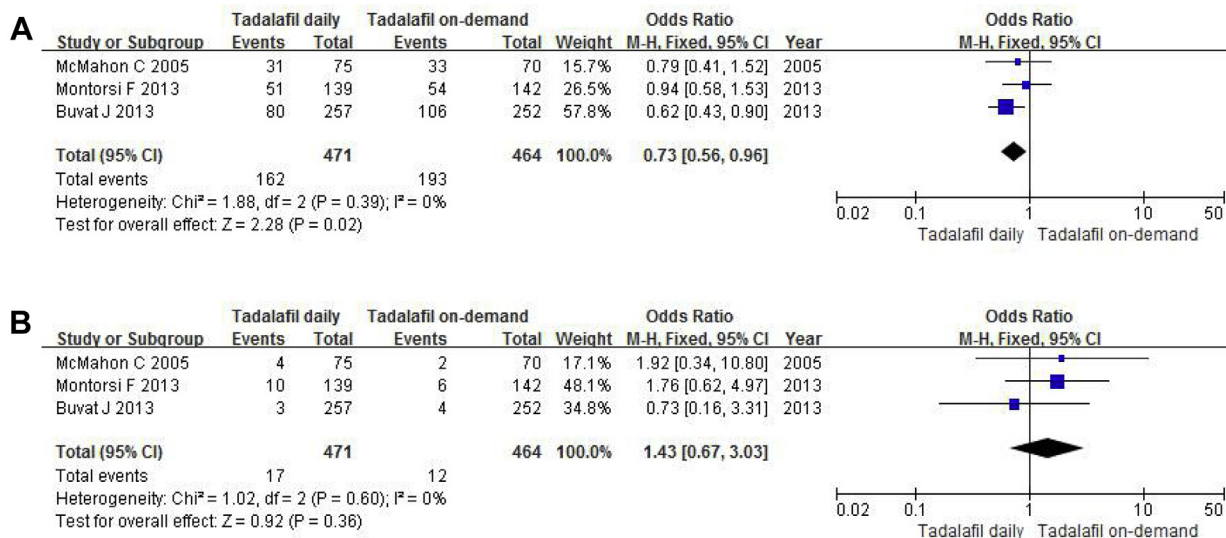

Figure 5. Forest plots showing number with (A) any treatment-emergent adverse event and (B) discontinuation due to adverse events. df, degrees of freedom; M−H, Mantel−Haenszel.
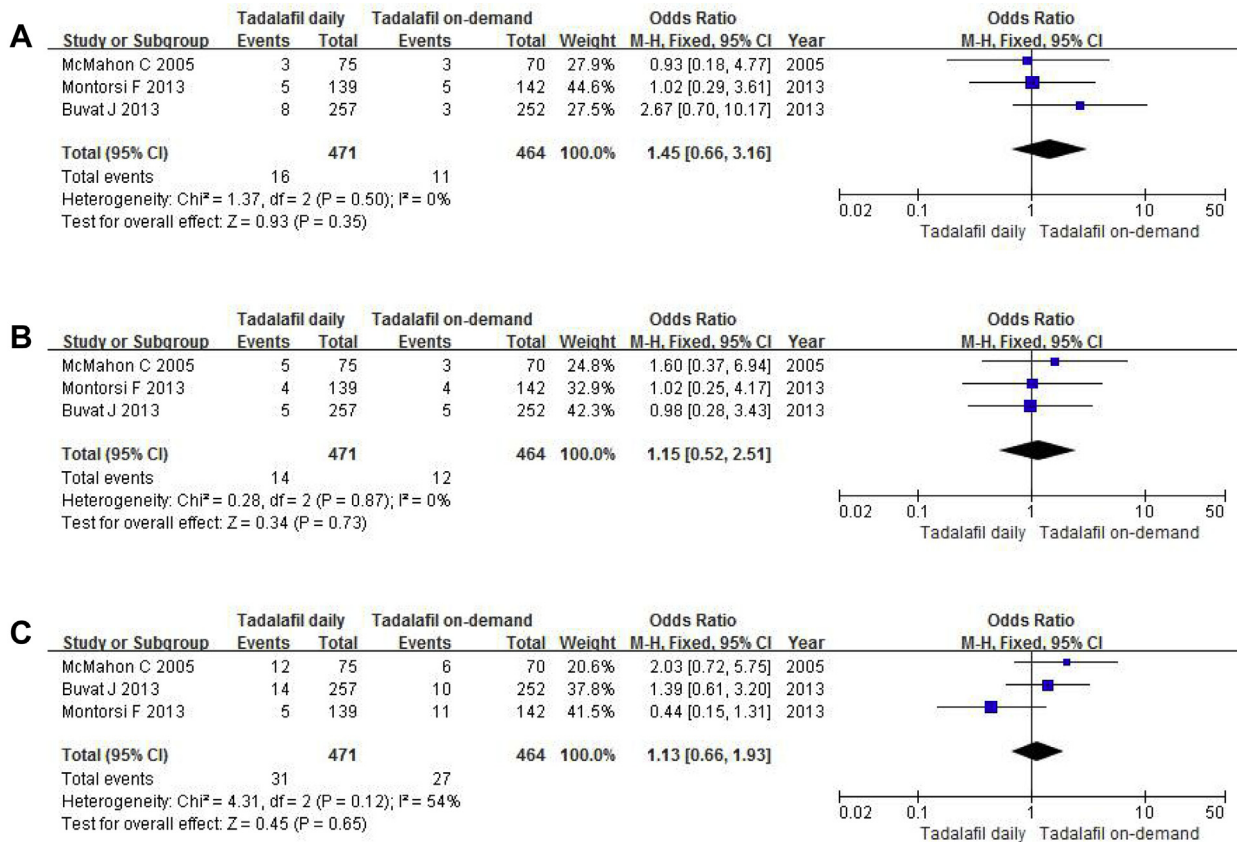
Figure 6. Forest plots showing number with (A) myalgia, (B) back pain, and (C) headache. df, degrees of freedom; M−H, Mantel−Haenszel.

Discontinuation due to AEs

3 RCTs accessed the meaning of discontinuation due to AEs with a sample size of 935 patients (471 in the tadalafil daily group and 464 in the tadalafil on-demand group). The OR was 1.43 and 95% CI was 0.67−3.03 (P = .36; Figure 5B). This result suggested that the tadalafil daily group had the same incidence in discontinuation due to AEs compared with the tadalafil on-demand group.

Myalgia, Back Pain, and Headache

3 RCTs with a sample of 935 patients (471 in the tadalafil daily group and 464 in the tadalafil on-demand group) analyzed the severity of related pain after taking medicine. A fixed-effects model showed no statistical significance between the tadalafil daily group and the tadalafil on-demand group http://dict. youdao.com/javascript:void(0);in the occurrence rate of myalgia (OR = 1.45; 95% CI = 0.66−3.16; P = .35), back pain
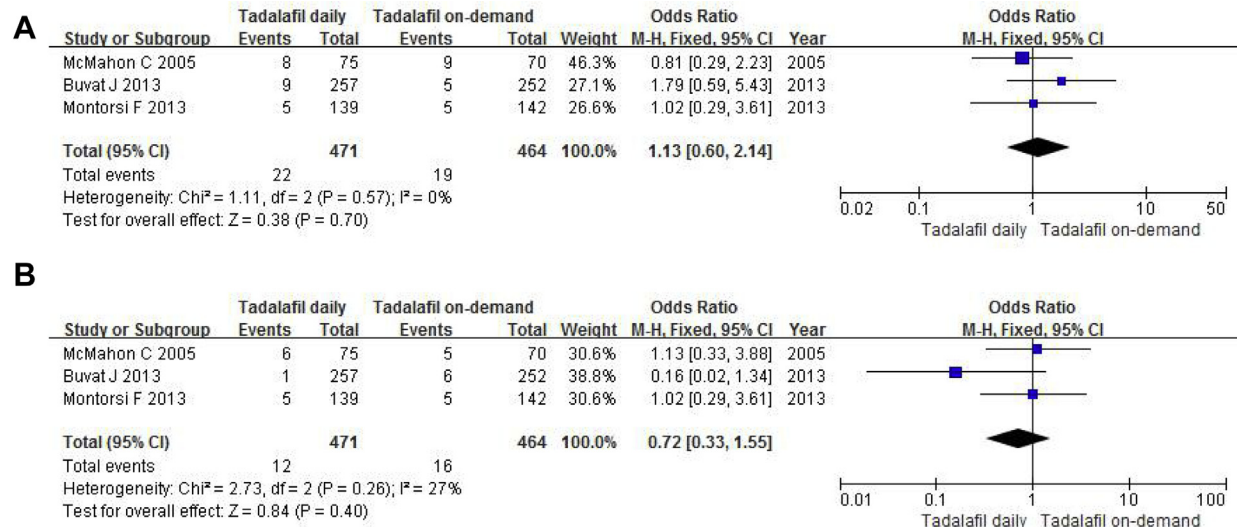

Figure 7. Forest plots showing number with (A) dyspepsia and (B) nasopharyngitis. df, degrees of freedom; M−H, Mantel−Haenszel.

(OR = 1.15; 95% CI = 0.52−2.51; P = .73), and headache (OR = 1.13; 95% CI = 0.66−1.93; P = .65; Figure 6A, B, C).

Dyspepsia and Nasopharyngitis

3 RCTs with a sample of 935 participants accessed the severity of dyspepsia and nasopharyngitis. The tadalafil daily group had no significant difference compared with the tadalafil on-demand group in rate of dyspepsia (OR = 1.13; 95% CI = 0.60−2.14; P = .70) and nasopharyngitis (OR = 0.72; 95% CI = 0.33−1.55; P = .40; Figure 7A, B).

DISCUSSION

Currently, many trials have confirmed the effectiveness of tadalafil once-daily and on-demand vs control group in the treatment of ED.[18,19] Tadalafil, a PDE5 approved by the U.S. Food and Drug Administration, has unique pharmacokinetic characteristics with a slower onset and longer effect lasting up to 36 hours.[20] In view of these unique pharmacokinetics, alternative dosage regiments have been proposed, including daily or on-demand doses. Some data suggested that partners might prefer the participants to take it daily rather than on-demand.[21] Although 12-week short-term evaluation comparing the 2 treatments is available, long-term efficacy and safety of the 2 kinds of treatments are unknown.[9,22]

We performed this meta-analysis for 4 studies, including 1,035 participants, to compare the efficacy and safety of tadalafil daily compared with tadalafil on-demand in treating men with ED after at least 24 weeks of long-term treatment. The analysis found that tadalafil daily had a greater improvement than tadalafil on-demand in terms of IIEF-EF, SEP2, and SEP3 in treating ED after at least 24 weeks of treatment. However, this result is somewhat different from previous meta-analysis of 12 weeks short-term treatment. Bansal et al[9] showed that once-a-day tadalafil does not provide a clinically significant increase in IIEF-EF scores when compared to on-demand tadalafil after 12 weeks treatment cycle. However, our study found that patients who needed long-term treatment had an advantage to take tadalafil daily rather than on-demand. More long-term RCTs are needed to confirm this finding, and treatment cycle should be the greater than or equal to at least 1 year.

For the regimen of tadalafil on-demand, the correlation between medication and intercourse could have significant psychological impact for men with ED. These psychological factors can affect patient's sexual performance, self-confidence, and QOL. The half-life of tadalafil may be an important factor in affecting psychological attention, in theory, tadalafil daily could maintain a longer effective plasma concentration than tadalafil on-demand, allowing patients to feel ready to have sex at all times and making them separate drug ingestion from sexual activity.[23] Based on these considerations, psychosocial outcomes seem to be related to the dosing regimen for tadalafil.

The Psychological and Interpersonal Relationship Scales were evaluated specifically by related clinical studies, including sexual self-confidence, spontaneity, and time concerns.[24,25] Statistical analysis found that tadalafil once-a-day was superior to tadalafil on-demand with statistical significance in the time concerns domain.[22,24,25] The generation of ED involves both physiological and psychological factors, in recent years, more and more attention has been paid to the psychological aspects of ED diagnosis and management.[26,27] PDE5 inhibitor can improve patient's sexual confidence by directly improving erectile function and indirectly improving spontaneity and reduced focus on time.[28]

Instructions regarding correct administration of tadalafil were summarized based on the product characteristics and the European Association of Urology guidelines on male sexual dysfunction: 1 tablet per day at approximately the same time every day (tadalafil daily); 1 tablet at least 30 minutes or approximately 1 hour before sexual activity, but no more than 1 tablet per day (tadalafil on-demand).

For safety, the study showed that tadalafil on-demand had a higher incidence of any treatment-emergent AE compared with tadalafil daily. In terms of discontinuation due to AEs, myalgia, back pain, headache, dyspepsia, and nasopharyngitis, there were no significant differences between the 2 treatments. Based on our analysis, it is strongly recommended that the physician explains to the patient the potentially serious side effects of long-term tadalafil on-demand before adopting this treatment. The scheme of tadalafil daily should be recommended for those who need long-term medication due to the relatively small incidence of side effects associated with the treatment.

The incidence of AE for PDE5 inhibitors is greater than placebo, but PDE5 inhibitors are generally well-tolerated for the treatment of ED.[29] The most common AEs cover headache, flushing, nasal congestion, nasopharyngitis, and dyspepsia, which is the effect of vasodilation on capillary smooth muscle in other parts of the body.[30] A network analysis suggested that PDE5 inhibitors were well-tolerated after 12 weeks of short-term treatment and no significant difference was found in safety between the 2 treatments.[31]

Although tadalafil daily provides a preferable therapeutic effect for ED with a lower incidence of treatment-emergent side effects, patients had personal preferences for different regimen for some reasons. 1 RCT[14] reported that 72% of patients chose the daily dosing regimen and 28% patients chose the on-demand dosing regimen. One possible reason for a large number of patients who were inclined to the daily dosing regimen is that tadalafil was freely supplied to 27.6% patients in this article, who were able to ignore the higher cost of taking tadalafil daily. For showing the adherence of treatment to tadalafil daily or on-demand in patients with ED without any exposure to PDE5 inhibitors, 1 RCT[17] found that the proportion of patients who replaced the scheme in the tadalafil daily group and the tadalafil on-demand group were 43.2% and 31%, respectively.

Above all, tadalafil daily provides a preferable therapeutic effect for ED with a lower incidence of treatment-emergent side effects relative to tadalafil on-demand after at least 24 weeks of long-term treatment.

We must acknowledge the limitations of this meta-analysis. We note that the quality of these studies is flawed, primarily in terms of study design, patient selection, blinding, difference in tadalafil doses, and severity of the ED. Therefore, the results of meta-analysis should be interpreted carefully. However, those articles included in this study were all RCTs to reinforce the findings. Second, IIEF-EF, male preference, compliance, and persistence are highly heterogeneous. We investigated the long-term efficacy and tolerance of tadalafil on-demand and tadalafil daily, and selection bias, subjective factors, and publication bias may also affect the final results of our study. More high-quality RCTs with suitable study cohorts are needed to ascertain the efficacy and tolerance of tadalafil daily and tadalafil on-demand in treating men with ED after at least the 24-week treatment cycle.

CONCLUSION

This meta-analysis suggests that tadalafil daily provides a preferable therapeutic effect for ED with a lower incidence of treatment-emergent side effects relative to tadalafil on-demand after at least 24 weeks of long-term treatment.

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