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REVIEW

Efficacy and safety of phosphodieterase-5 inhibitors for treatment of erectile dysfunction secondary to spinal cord injury: a systemic review and meta-analysis

D-D Jia, W-B Shuang, T Cheng, X-M Jia and M Zhang

Study design: Systemic review
Objective: We carried out a systematic review and meta-analysis to assess the efficacy and safety of phosphodieterase-5 (PDE5) inhibitors on erectile dysfunction (ED) secondary to spinal cord injury (SCI).
Methods: A literature review was performed to identify all published randomized, double-blind, placebo-controlled trials of PDE5 inhibitors for treatment of ED secondary to SCI. The search included the following database: MEDLINE, EMBASE and the Cochrane Library. The outcomes and complications analyzed involved the Global Efficacy Question (GEQ), sexual encounter profile diary question 2 and 3 (SEP2 and SEP3) and adverse events. All statistical analysis was performed using Stata 12.0 software (Stata Corp., College Station, TX, USA).
Results: Six publications were used in analysis, including six randomized controlled trials that compared PDE5 inhibitors with placebo. Compared with placebo, PDE5 inhibitors were associated with significant improvements in GEQ (OR 11.997, 95% CI 8.073–17.830, $P<0.0001$), SEP2 (RR 1.847, 95% CI 1.561–2.185, $P<0.0001$) and SEP3 (RR 2.738, 95% CI 2.084–3.598, $P<0.0001$). Despite significant greater incidences of some adverse events observed (headache: RR 3.717, 95% CI 2.309–5.982, $P<0.0001$; flushing: RR 9.281, 95% CI 2.858–30.147, $P<0.0001$; gastrointestinal discomfort: RR 9.064, 95% CI 2.116–38.827, $P=0.003$), most adverse events were mild to moderate and transient.
Conclusions: This systematic review and meta-analysis indicate that PDE5 inhibitors are effective and well tolerated to treat ED secondary to SCI compared with placebo, as measured by response to GEQ, SEP2, SEP3 and incidence of adverse events. PDE5 inhibitors could be considered as the first choice in the treatment of ED patients with SCI.
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INTRODUCTION

Approximately 11 000 new cases are estimated to suffer from spinal cord injury (SCI) in America each year and 60% of them are between 16 and 30 years of age. Moreover, men account for 82% of all patients with SCI.[1,2] Erectile dysfunction (ED) is a common condition in individuals with SCI.[3] A high prevalence of ED is reported in about 80% of SCI patients.[4] It is an especially bothersome condition in young men who usually had an active sexual activity before their accident.[5]

ED is defined as the persistent inability to achieve or maintain a penile erection for satisfactory sexual performance.[6] Most men with SCI have some type of penile erection, but it is usually not hard enough or does not last long enough for sexual life.[1] ED not only often results in disorder of self-esteem but also deteriorates partner relationship. Hence, ED has a negative effect on the life of men and their sexual partner.[7] Health-care providers deem sex life significant in the process of rehabilitation after SCI and give high priority to improving sexual activity for subjects with SCI.[8,9]

Nitric oxide (NO) released by nonadrenergic-noncholinergic nerves in the penis has an important role in initiating and maintaining of the penile erection process.[10,11] NO diffuses to smooth where it augments the formation of cyclic guanosine monophosphate, which acts as a second messenger for engorgement of penile vasculature and penile erection.[12,13] Phosphodieterase-5 (PDE5) could facilitate the breakdown of cyclic guanosine monophosphate in the cavernosal smooth muscle where PDE5 is sufficient.[14] The PDE5 inhibitors function by inhibiting the catalytic site of PDE5, an enzyme that could hydrolyze cyclic guanosine monophosphate. As a result, with a corresponding increase in cavernosal tumescence and rigidity, smooth muscle relaxation is enhanced and blood inflow into the corpora cavernosa.[6,15] As the first oral selective phosphodieterase type5 (PDE5) inhibitor, the introduction of sildenafil in 1998 is an important advance in the treatment of ED.[16] Two other PDE5 inhibitors, vardenafil and tadalafil, were also developed in recent years.[17] The oral treatment with PDE5 inhibitors is considered the least invasive method.[18] PDE5 inhibitors have also changed the treatment of ED in SCI patients, becoming the preferred treatment in subjects with SCI since the introduction of sildenafil because of their ease of use and effectiveness.[19–21] Nevertheless the role of PDE5 inhibitors to treat ED caused by SCI has not been well assessed. It is

Department of Urology, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China
Correspondence: Dr W-B Shuang, Chief Physician, Department of Urology, First Hospital of Shanxi Medical University, No. 85, JieFang South Road, Yingze District, Taiyuan 030001, Shanxi Province, P.R. China.
E-mail: shuangweibing@126.com
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still challenging to identify the efficacy and safety of PDE5 inhibitors in SCI patients suffering from ED. In this case, superior evidence-based medicine support is absent in treatment of ED in SCI subjects. Thus, we aimed to analyze highly selected quality randomized controlled trials (RCTs) with meta-analytic methodology and resolve question of the efficacy and safety of PDE5 inhibitors for ED secondary to SCI.

MATERIALS AND METHODS

Search strategy

The pertinent studies were obtained by searching Medline, Embase and Cochrane Library up to March 2015. Search keywords used were ED, SCI, phosphodieterase type 5 inhibitors, PDE5, PDE5-I, sildenafil, vardenafil, tadalafil, avanafil, udenafil and mirodenafil. Furthermore, the references of included trials and relevant review articles were searched to identify additional potentially pertinent studies. We did not apply any methodological search filters and date or language limits. Two reviewers independently employed this search strategy to screen all titles and abstracts for identifying eligible trials.

Inclusion criteria and trials selection

RCTs meeting the following criteria were included: (i) the study design involved treatment with PDE5 inhibitors; (ii) the accurate data were provided for analysis, including the total number of subjects and values of necessary outcomes like the Global Efficacy Question (GEQ), sexual encounter profile diary question 2 and 3 (SEP2 and SEP3) or incidences of adverse events; and (iii) the full-text of trial could be appraised. The most recent publication was adopted for meta-analysis if the same study was reported in different journals or years. We adopted each trial with multiple experiments conducted by the same group of searchers. We contacted authors if the data we need were all included in the articles. Two authors assessed literatures meeting the inclusion criteria independently and discrepancy was resolved by consensus with another author. A flow diagram of trial selection process is presented in Figure 1.

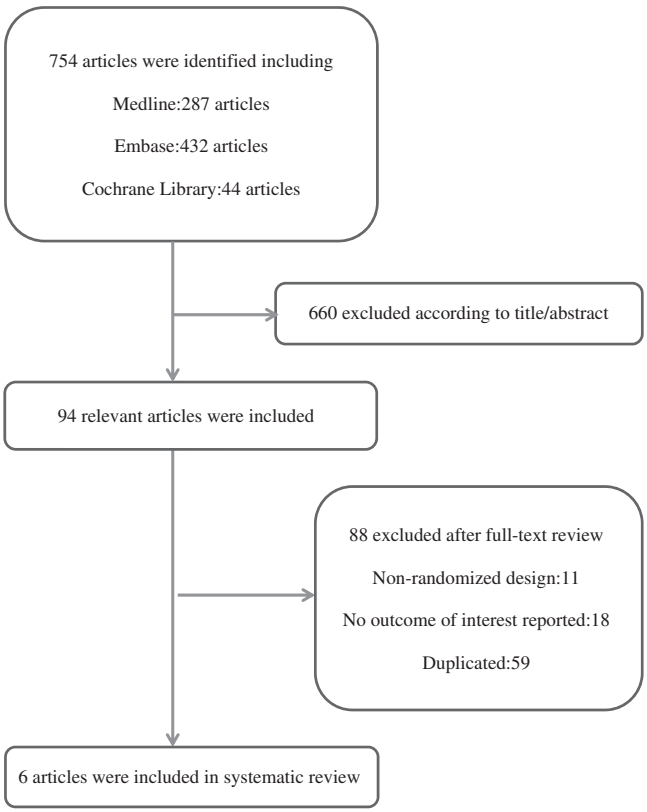

Figure 1 A flow chart of the study selection process. A full color version of this figure is available at the *Spinal Cord* journal online.

Quality assessment

The methodological quality of the included trials was appraised by two reviewers based on the Cochrane Collaboration Reviewers' Handbook for Systemic Reviews of Interventions.[22] The quality assessment of retrieved RCTs involved evaluation of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias. The judgement ('Low risk ', 'High risk' or 'Unclear risk') is made for each entry. According to the quality assessment criteria, we assigned each trial to the three different quality categories. If all quality criteria were completely met and the study was considered to have a low risk of bias, we ranked it as class A; if one or more of quality criteria were not adequately met or were unclear and the trial was deemed to have a moderate risk of bias, we ranked it as class B; if one or more of the criteria were not included or not met and the trial was deemed to have a high risk of bias, we ranked it as class C. Discrepancy was resolved by consensus with a third reviewer.

Data extraction

Data extraction was performed independently by two reviewers with predesigned data extraction forms. The following information was extracted for each trial: (i) participants: diagnostic criteria, number of each group, age, severity of SCI, withdrawal and lost to follow-up; (ii) method: study design, randomized methods, blinding method and allocation concealment method; (iii) intervention: details of treatment, such as type, dose and treatment duration; (iv) outcomes: the response to the GEQ, the response to the SEP2 and SEP3 and all reported adverse effects; (v) other: country and publication year. Disagreements were resolved via consultation with another author.

Statistical analysis and meta-analysis

All statistical analysis was performed using Stata 12.0 software (Stata Corp., College Station, TX, USA). All data we extracted were dichotomous data; hence, we estimated the odds ratio (OR) or relative risk (RR) for outcomes and complications. A 95% confidence interval (95% CI) was used. We used the χ^2 test and the I^2 test to appraise statistical heterogeneity between included trials. An I^2 statistic of $<50\%$ suggests that low heterogeneity exists among studies, an I^2 statistic of 50–75% suggests that moderate heterogeneity exists, and I^2 statistic of $>75\%$ suggests that high heterogeneity exists.[23] If I^2 statistic is more than 50%, it was deemed to have substantial statistical heterogeneity in included studies. Whether a fixed-effects model was used mainly depends on the results of the I^2 test for heterogeneity. We chose a fixed-effect model for meta-analysis if the studies were homogeneous. Otherwise, a random-effect model was used and a sensitivity analysis was performed to explore the reliability of results. A subgroup analysis was performed simultaneously to explore possible heterogeneity by the types of PDE5 inhibitors, doses of drugs, duration of treatment and severity of ED if data were sufficient. In the case of excessive heterogeneity, we only performed descriptive analysis instead of meta-analysis.

RESULTS

Study identification and selection

A total of 754 studies were selected in the initial database search, and 660 studies were excluded based on title and abstract of articles. Fifty-nine studies were excluded on account of duplicate, and 29 studies were excluded because they did not meet our inclusion criteria after reading full-text. In all, six articles[24–29] involving six RCTs were adopted for analysis: four RCTs that compared sildenafil with placebo, one RCT that compared vardenafil with placebo and one RCT that compared tadalafil with placebo. The baseline characteristics of the trials included in our meta-analysis are listed in Table 1.

Quality of the individual studies

All six RCTs were double blinded and the randomization process was described. We summarized the results of all the risk of bias assessment in Figure 2. The level of quality of the two trials was C, and the level of the rest was B.

Table 1 Characteristics of trials included in systematic review

Study	*Year*	*Location of trial*	*Age (year)*	*Therapy in experimental group*	*Therapy in control group*	*Sample size (experimental)*	*Sample size (control)*	*Duration of treatment (week)*	*Dosage*	*Withdrawal*
Khorrami *et al.*[24]	2010	Iran	46.7 (40–45)	Sildenafil	Placebo	59	46	24	50 mg/100 mg	0
Maytom *et al.*[25]	1999	UK	33 (21–49)	Sildenafil	Placebo	12	14	4	50 mg	1
Hultling *et al.*[26]	1999	Europe, Australia	38 (19–36)	Sildenafil	Placebo	175	174	6	25 mg/50 mg/100 mg	10
Ergin *et al.*[27]	2008	Turkey	38.9±8	Sildenafil	Placebo	50	50	6	50 mg	4
Giuliano *et al.*[28]	2006	North America, Europe, Asia Pacific	39.5 (18–80)	Vardenafil	Placebo	168	156	12	5 mg/10 mg/20 mg	94
Giuliano *et al.*[29]	2007	France, Germany, Italy, Spain	38 (18–66)	Tadalafil	Placebo	136	41	12	10 mg/20 mg	23

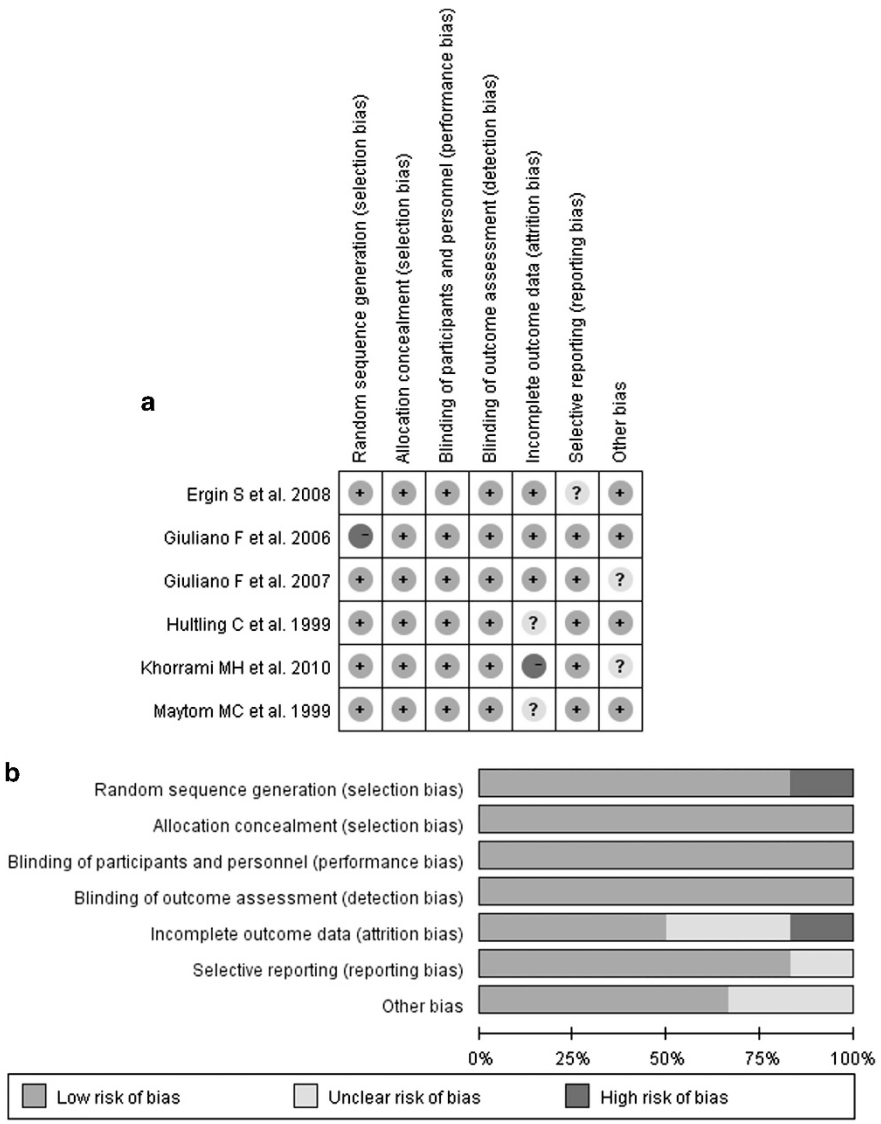

Figure 2 (**a**) Risk of bias summary: review authors' judgments about each risk of bias Item for each included study. (**b**) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. A full color version of this figure is available at the *Spinal Cord* journal online.

Efficacy end points

Four trials reported the response to GEQ ('Has the treatment you have been taking during this study improved your penile erection'). A total of 366 patients and 261 patients were involved, respectively, in trials to compare the efficacy of PDE5 inhibitors versus placebo. The heterogeneity test indicated no significant heterogeneity ($P=0.191$;

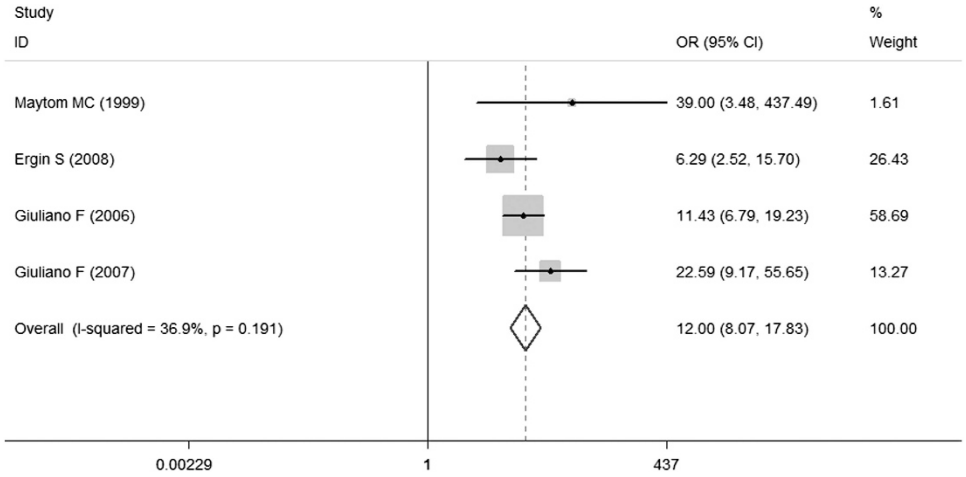

Figure 3 Forest plot diagram showing the response to GEQ ($P=0.191$, $I^2=36.9\%$, OR 11.997, 95% CI 8.073–17.830). A full color version of this figure is available at the *Spinal Cord* journal online.

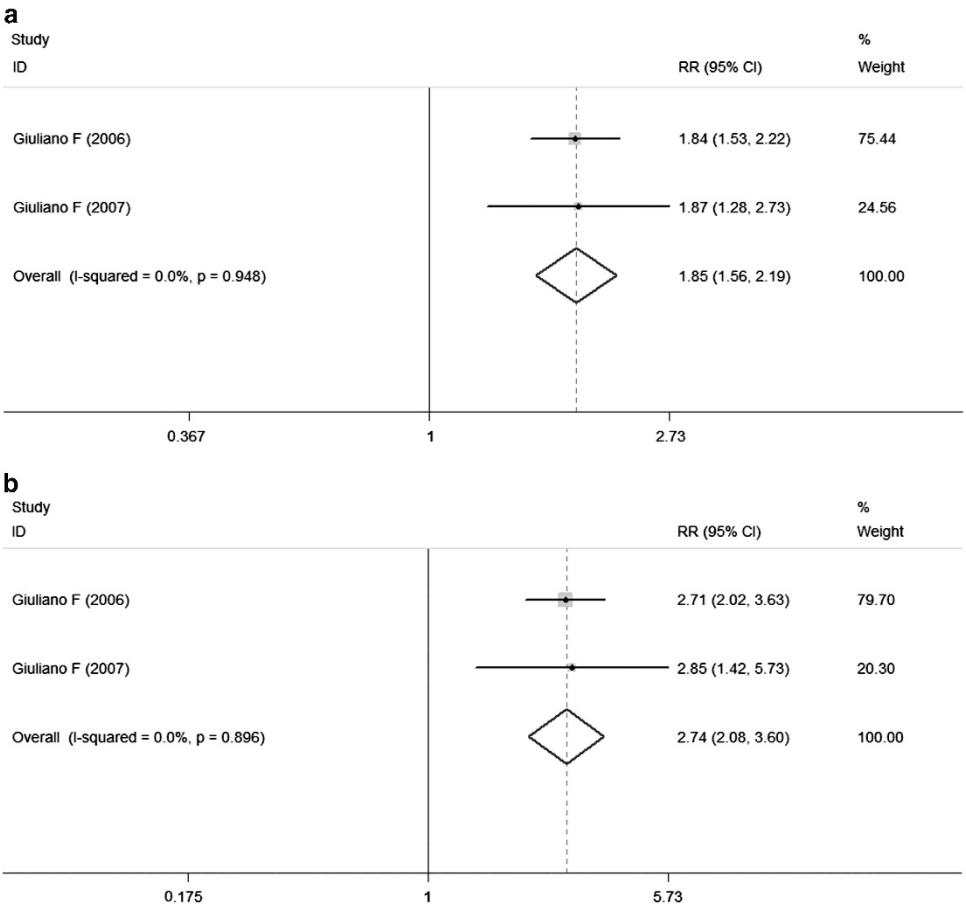

Figure 4 Forest plot diagram showing the response to (**a**) SEP2 ($P=0.948$, $I^2=0.0\%$, RR 1.847, 95% CI 1.561–2.185) and (**b**) SEP3 ($P=0.896$, $I^2=0.0\%$, RR 2.738, 95% CI 2.084–3.598). A full color version of this figure is available at the *Spinal Cord* journal online.

$I^2=36.9\%$), and hence the fixed-effect model was used. The pooled estimate of the OR was 11.997, the 95% CI was 8.073–17.830 and $P<0.0001$ (Figure 3). This result suggests that PDE5 inhibitors show statistically greater improvement in response to GEQ compared with placebo.

Only two trials contributed to SEP2 and SEP3 analysis. Trials comparing the efficacy of PDE5 inhibitors versus placebo involved 334 patients and 235 patients, respectively. Sexual Encounter Profile is deemed as a diary in which patients' responses ('Yes/no') concerning specific aspects of sexual encounter were reported. The SEP2 asked 'Were you able to insert your penis into your partner's vagina?', and the SEP3 asked 'Did your penile erection last long enough for you to have successful intercourse?' No heterogeneity for both questions was observed in pooled analysis (SEP2: $P=0.948$, $I^2=0.0\%$; SEP3:

Table 2 Common reported treatment-related adverse events in each group

Study	Year	Total	PDE5 inhibitor			Total	Placebo		
			Headache	Flushing	Gastrointestinal discomfort		Headache	Flushing	Gastrointestinal discomfort
Khorrami *et al.*[24]	2010	59	8	4	4	46	0	0	0
Maytom *et al.*[25]	1999	12	4	—	1	14	1	—	0
Hultling *et al.*[26]	1999	175	30	12	5	174	8	2	0
Giuliano *et al.*[28]	2006	200	29	12	7	201	8	0	0
Giuliano *et al.*[29]	2007	144	12	—	0	44	2	—	0

$P=0.896$, $I^2=0.0\%$), and hence the fixed-effect model was used. The pooled results showed that a much greater number of patients in the PDE5 inhibitor group to respond to SEP2 and SEP3 positively (SEP2: RR 1.847, 95% CI 1.561–2.185, $P<0.0001$; SEP3: RR 2.738, 95% CI 2.084–3.598, $P<0.0001$; Figure 4).

Adverse events

Adverse events of PDE5 inhibitors and relevant data were reported in five trials. Studies comparing adverse events of PDE5 inhibitors versus placebo included 590 patients and 479 patients, respectively. The individual adverse events such as headache, flushing and gastrointestinal discomfort were analyzed (Table 2). Nevertheless, flushing, one of the adverse events, was only mentioned in three articles. No significant heterogeneity for incidence of headache, flushing and gastrointestinal discomfort was found in the pooled analysis (headache: $P=0.784$, $I^2=0.0\%$; flushing: $P=0.652$, $I^2=0.0\%$; gastrointestinal discomfort: $P=0.915$, $I^2=0.0\%$), and hence the fixed-effect model was used. Incidence of headache, flushing and gastrointestinal discomfort showed significant high incidence in the PDE5 Inhibitor group (headache: RR 3.717, 95% CI 2.309–5.982, $P<0.0001$; flushing: RR 9.281, 95% CI 2.858–30.147, $P<0.0001$; gastrointestinal discomfort: RR 9.064, 95% CI 2.116–38.827, $P=0.003$; Figure 5). However, most adverse events were mild to moderate and transient.

Publication bias

Visual inspection of the funnel plot for response to GEQ and incidence of headache and gastrointestinal discomfort found a slightly asymmetrical distribution. However, according to Begg's and Egger's test, no evidence of substantial publication bias existed among the included trials for response to GEQ (Begg's test, $P=1.000$; Egger's test, $P=0.610$; Figure 6), response to SEP2 (Begg's test, $P=1.000$), response to SEP3 (Begg's test, $P=1.000$), incidence of headache (Begg's test, $P=0.462$; Egger's test, $P=0.626$, Figure 7), incidence of flushing (Begg's test, $P=1.000$; Egger's test, $P=0.509$) and incidence of gastrointestinal discomfort (Begg's test, $P=0.089$; Egger's test, $P=0.073$).

DISCUSSION

To our knowledge, this is first meta-analysis with RCTs to assess the efficacy and safety of PDE5 inhibitors for ED caused by SCI. A recent publication by Nicole Rizio reviewed the medical literature in 2000–2010. Nicole Rizio considered that sildenafil, tadalafil and vardenafil have proved to be comparably efficacious in the treatment of ED in men with SCI, as all studies included had shown a statistical increase in the international index of erectile function scores.[30] Nevertheless, this review did not employ a meta-analysis methodology.

Most patients with SCI require some supportive treatment for their ED because their penile erections are often less rigid and have more difficulty to maintain.[31,32] A variety of management options could be adopted for individuals with SCI.[33] However, therapies for ED caused by SCI remain challenging, and PDE5 inhibitors, vacuum devices, penile implants, intraurethral prostaglandins, percutaneous perineal electrostimulation, transdermal nitroglycerin, intracavernous injection of papaverine and some other therapies are still under debate.[33–39]

The aim of this systematic review focused on comprehensively appraising efficacy and safety of PDE5 inhibitors in patients with SCI. In the present review, a large portion of ED patients secondary to SCI greatly benefited from PDE5 inhibitors (sildenafil, vardenafil or tadalafil). Overall, patients receiving PDE5 inhibitors had a higher percentage of positive response to GEQ, compared with men allocated to the placebos groups. In addition, significant improvements were found in key secondary efficacy end points of SEP2 and SEP3 for PDE5 inhibitor treatment groups. Therefore, our results show that PDE5 inhibitors could significantly improve erectile function in SCI patients compared with placebo. All researchers instructed patients to take PDE5 inhibitors as needed approximately 1 h or at least 45 min prior to sexual activity, and no trial using once-a-day administration was included. Whether once-a-day administration of PDE5 inhibitors could improve penile erection is still obscure, and new trials are needed to address this issue.

Safety data from the trials in this meta-analysis suggest that PDE5 inhibitor administration was generally well tolerated. Despite significant greater incidences of some adverse events observed, most adverse events were mild to moderate and transient. The most commonly reported adverse events were headache, flushing and gastrointestinal discomfort. Only four cases of discontinuation due to serious adverse events were reported in about 600 men receiving PDE5 inhibitors included in this review. Moreover, it is reported in a study that the frequency of these PDE5 inhibitor-characteristic adverse events declined over the course of study.[28] A majority of included RCTs suggested no clinically significant changes in heart rate, blood pressure and laboratory tests in the PDE5 inhibitors groups.

Information on response of GEQ was primarily based on four RCTs,[25,27–29] and the data on response of SEP were collected from two RCTs,[28,29] and the data on incidence of adverse events synthesized from five articles.[24–26,28,29] The reason why we did not analyze efficacy of PDE5 inhibitors with international index of erectile function was that they did not report values of standard deviation, although it has been deemed to have a high degree of sensitivity and specificity for extrapolating treatment-related changes in the erectile function.[40]

The data in studies included in this meta-analysis all derived from randomized, double-blind, placebo-controlled trials. On the basis of

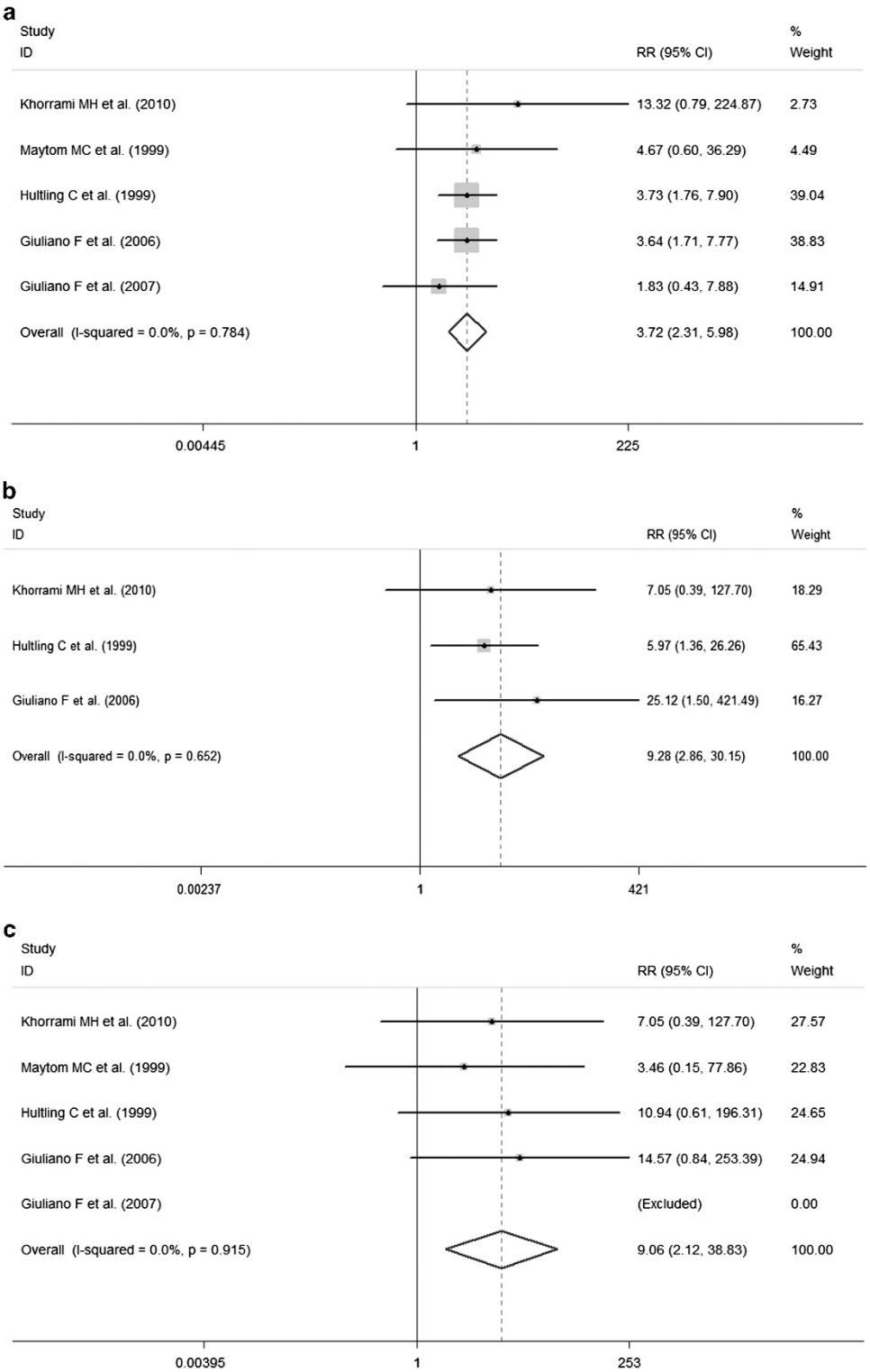

Figure 5 (**a**) Forest plot diagram showing (a) headache incidence ($P=0.784$, $I^2=0.0\%$, RR 3.717, 95% CI 2.309–5.982), (**b**) flushing incidence ($P=0.652$, $I^2=0.0\%$, RR 9.281, 95% CI 2.858–30.147) and (**c**) gastrointestinal discomfort incidence ($P=0.915$, $I^2=0.0\%$, RR 9.064, 95% CI 2.116–38.827). A full color version of this figure is available at the *Spinal Cord* journal online.

the quality assessment scale developed, the quality of the individual trials in the meta-analysis was conforming. The results of this review acquire great importance from everyday clinical practice. However, some limitations of the present results should be mentioned. First, we did not comment on the differences in efficacy and safety among three PDE5 inhibitors (sildenafil, vardenafil and tadalafil) because no direct comparisons were made in these six trials. Second, as the longest duration of the therapy was 24 weeks, long-term efficacy and safety of

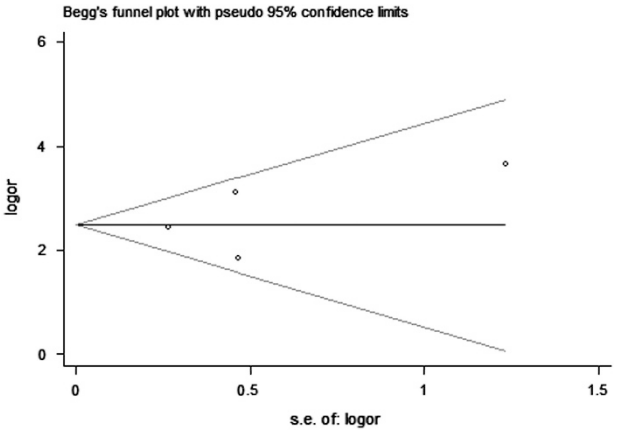

Figure 6 Begg's funnel for the visual assessment of overt publication bias for response to QEQ.

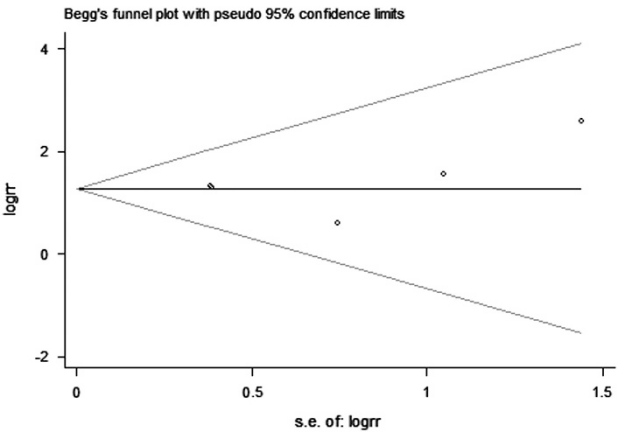

Figure 7 Begg's funnel for the visual assessment of overt publication bias for headache incidence.

PED5 inhibitors cannot be detected. Third, only six RCTs with a limited number of patients assessing the efficacy and safety of PDE5 inhibitors and the data from unpublished trials were not included in the analysis. In addition, we did not determine whether the characteristics of patients are potential risk factors (age, body mass index and other baseline parameters) that could influence the results. Finally, the efficacy of daily treatment with PDE5 inhibitors was not assessed because of a lack of relevant studies. Futher high-quality trials with larger samples from all over the world are proposed to learn more about the efficacy and safety of the therapies for ED secondary to SCI.

CONCLUSIONS

This systematic review and meta-analysis indicate that PDE5 inhibitors are effective to treat ED secondary to SCI compared with placebo, as measured by response to GEQ, SEP2 and SEP3. PDE5 inhibitors can be deemed as the first choice in the treatment of ED patients with SCI. In addition, adverse events were transient and serious adverse events were few, which showed that PDE5 inhibitors were well tolerated. Further high-quality studies are expected to evaluate the long-term outcomes, relationship between the outcomes and characteristic of patients and efficacy of once daily PDE5 inhibitors in treatment of ED secondary to SCI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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