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Effectiveness and Safety of PDE5 Inhibitors for Men with Erectile Dysfunction Caused by Spinal Cord Injury

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Authors' contributions

This work was carried out in collaboration between all authors. Authors HD and YT designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors YD and ZN managed the literature searches. Authors LY and BC collected the data. Authors YT, YD and ZN performed the statistical analyses. Authors HD and YT participated in critical revision of the manuscript. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Aims: The objective of this review was to assess the effectiveness of phosphodiesterase type 5 (PDE5) inhibitors in men with erectile dysfunction (ED) and spinal cord injury (SCI).
Methodology: The following databases were sought up to May 2015: PubMed, Google scholar, EMBASE and Cochrane Library. We performed a meta-analysis of all available randomised controlled trials. We used odds ratios (ORs) to assess the strength of the association, and 95% confidence intervals (CIs) gave a sense of the precision of the estimate. Statistical analyses were performed by Review Manager, version 5.0.
Results: After searching and screening the relevant articles, ten studies were included and assessed the effectiveness of PDE5 inhibitors in men with erectile dysfunction and spinal cord injury. The pooled results showed that sildenafil significantly improved erection compared with

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placebo in ED patients with SCI (OR = 5.96, 95% CI [3.36–10.55], P < 0.00001) and there was no statistical difference compared incomplete injury group with complete injury group (OR = 0.73, 95% CI [0.38–1.43], P=0.36). It is evident that compared upper motor neuron with lower motor neuron, there were better responsive rates in sildenafil(OR = 11.56, 95% CI [2.88–46.36], P=0.0006). Because of lacking studies and data, we could not perform meta-analysis for other PDE5 inhibitors. The commonly reported adverse effects (AEs) were headache, flushing, dizziness and urinary tract infection in these studies. No severe adverse events were found.

Conclusion: Current evidence suggests that sildenafil is effective treatment for ED patients with SCI. In future, we need more high quality randomized controlled trials (RCTs) to confirm these findings and evaluate the effectiveness of other PDE5 inhibitors.

Keywords: PDE5 inhibitors; erectile dysfunction; spinal cord injury; sildenafil.

1. INTRODUCTION

1.1 Description of the Condition

A traumatic spinal cord injury (SCI) is a lesion of neural elements of the spinal cord that can result in any degree of autonomic, motor and sensory deficit, as well as bowel dysfunction. The annual incidence of traumatic SCI in industrialised nations is approximately 15 to 40 cases per million [1-3]. The neurological deficit or dysfunction can be complete or incomplete, temporary or permanent. Because of the subsequent complications, individuals with an SCI may need lifetime follow up by specialists [4].

One of those subsequent complications is erectile dysfunction (ED), which is defined as the consistent or recurrent inability to achieve or maintain an erection sufficient for satisfactory sexual activity [5]. There are around 11,000 traumatic SCIs each year in the USA; approximately 80% in men. The average age at injury has increased to 42.6 years in recent years; however, SCIs still mainly affect young male population worldwide, resulting in negative physical, social, and psychological consequences [6-8]. Studies indicated that between 25% and 89.5% of males with SCI could have difficulties with erectile function [9-11]. These difficulties can include problems getting an erection, maintaining an erection, or both. Furthermore, a high proportion of men with SCI cannot ejaculate during sexual intercourse. SCI-related ejaculatory disorders are often responsible for infertility among that group [12]. Sexual dysfunction associated with SCI can also affect men's self-confidence [13].

In patients with SCIs, the degree of erectile function is mainly attributed to the location, nature, and extent of the lesion [14]. Considering the etiology and severity as well as concomitant comorbid conditions in men with spinal cord injury, the safe, effective and convenient therapies for treatment of ED caused by spinal cord injury are needed.

Numerous strategies have been tried to overcome this spinal cord injury complication. Treatment options for ED include oral medications, psychological management, vacuum constriction devices, intra cavernosal injections, transurethral drug delivery, penile prostheses, vascular surgery, and discontinuation of medications that can cause ED [15]. Men have reported a clear preference for oral medications and are considered first-line therapy. In recent years, three phosphodiesterase type 5 (PDE5) inhibitors, sildenafil (Viagra®), vardenafil (Levitra®) and tadalafil (Cialis®), have been introduced in the management of erectile dysfunction. Sildenafil citrate is the first orally active inhibitor of PDE5 to be approved by FDA, and widely used for the treatment of ED. Several new PDE5 inhibitors, tadalafil, vardenafil, udenafil and avanafil, which are similar in their pharmacologic action to sildenafil, have reported better tissue specificity and pharmacokinetic profiles than sildenafil. Some clinical trials have been conducted to examine the effect of PDE5 inhibitors in the treatment of erectile dysfunction with spinal cord injury [9,13,16-20]. Publications and reviews on erectile dysfunction in spinal cord injury patients also exist. Up to now, no formal systematic review and meta-analysis have been conducted to assess the management of ED with PDE5 inhibitors in patients with spinal cord injury.

2. METHODS CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

2.1 Types of Studies

Randomised controlled trials, in which treatment with PDE5 inhibitors were compared to controls,

in patients with ED and spinal cord injury. We also considered cross-over trial design (no wash-out period is required in this case due to the temporary nature of treatment interventions). Trials with interventions and follow-up period of any duration were included.

We excluded controlled randomised trials in which allocation to the treatment or control group was not truly random or in which treatment allocation was not concealed.

2.2 Types of Participants

Men with spinal cord injury and erectile dysfunction were included. Treatment for this disorder was in a prospective trial design in which at least one treatment option included PDE5 inhibitors.

2.3 Types of Interventions

Treatment for erectile dysfunction in spinal cord injury patients with a PDE5 inhibitor, orally administered at any regimen, in trials of any duration.

1. PDE-5 inhibitors

   a. sildenafil (Viagra®)
   b. vardenafil (Levitra®)
   c. tadalafil (Cialis®)
   d. udenafil
   e. avanafil

2. Comparison group

   a. no treatment
   b. placebo
   c. other PDE5 inhibitors
   d. other therapeutic options for erectile dysfunction in spinal cord injury patients

      i. psychosexual counselling
      ii. vacuum devices for inducing erection
      iii. hormonal manipulations
      iv. transurethral drug delivery - alprostadil with or without prazosin
      v. intra cavernosal injection of vasoactive agents - alprostadil or papaverine or phentolamine
      vi. penile prosthesis

2.4 Types of Outcome Measures

2.4.1 Primary outcomes

We defined our main outcome measure as the achievement of penile rigidity satisfactory for penetration and sufficiently prolonged to enable sexual intercourse to be completed. This will be assessed using the self-administered International Index of Erectile Function (IIEF), a 15-item questionnaire and validated measure of erectile function [21]. Each question was scored using a five point ordered categorical scale, with a score of one representing the worst response ('almost never'/'never') and a score of five representing the best response ('almost always'/'always').

2.4.2 Secondary outcomes

1. GAQ (Global Assessment Questionnaires)
2. SEP (Sexual Encounter Profile)
3. QOL (Quality of Life)
4. Adverse events
5. Morbidity due to the interventions

2.4.3 Search methods for identification of studies

2.4.3.1 Electronic searches

We used electronic search strategies to identify relevant trials (as defined under 'Types of studies'). The following electronic databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) 2015; PUBMED (2015); and EMBASE (2015). The search was performed without language restrictions.

2.4.4 Data collection and analysis

2.4.4.1 Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. Two reviewers (Ding Hui, Teng Yang) independently scanned the titles, abstract sections and keywords of every record retrieved. Full articles were retrieved for further assessment if the information given suggests that the study fulfilled the inclusion criteria and did not meet the exclusion criteria.

2.4.4.2 Data extraction

The extracted data included general information (such as author, title, publication, language of publication, year of publication, country, complete reference or source, contact details, duplicate publication, multiple publication, rural or city, single centre versus multi centre, setting, stated aim of the study, sponsor, ethic committee approval and description of conflict of interests), trial design, participants, the type of intervention, and outcome measures.

2.5 Statistical Analysis

Dichotomous outcomes results were measured by odds ratios (ORs) with 95% confidence intervals (CIs), the statistical significance of the summary OR was determined using the Z-test.

A chi-square-based Q statistics test and I^2-test were used to assess the heterogeneity between the studies. Heterogeneity was considered significant if $P < 0.05$. The value of $I^2$was used to assess the degree of heterogeneity ($I^2 < 25\%$, no heterogeneity; I^2 25%-50%, moderate heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity). The Mantel-Haenszel method (fixed-effects) and the DerSimonian-Laird method (random-effects) were used to estimate the pooled ORs. The quality of included RCTs were evaluated by using Jadad score [22]. Publication bias was assessed using inverted funnel plots. Funnel plot asymmetry was assessed using Egger's linear regression test. An asymmetric plot indicated possible publication bias. The significance of asymmetry was determined using the t test, and $P < 0.05$ was considered to indicate a significant publication bias. Meta-analyses were performed using Review Manager, version 5.0, software (The Cochrane Information Management System, http://ims.cochrane.org/revman) and Software STATA version 11.0 (Stata Corporation, College Station, TX, USA).

3. RESULTS

3.1 Study Characteristics

A total of ten studies [9,13,16,17,23-28] investigating the relationships between PDE5 inhibitors and ED with SCI met our inclusion criteria. The characteristics of each study are summarized in Table 1. These studies were published from 1998 to 2010. Seven studies reported sildenafil for ED with SCI, two studies reported vardenafil for ED with SCI; and two studies reported tadalafil for ED with SCI, respectively. In all the studies, the duration of treatment ranged from 4 weeks to 12 weeks, one RCT compared the efficacy of sildenafil with that of tadalafil. Two articles [13,16] were excluded because of repeat data published in previous study. Eight studies were included in the final analysis (Table 1). The Jadad scores of all included RCTs were less than 3.

3.2 Sildenafil

Four studies reported the efficacy of sildenafil in ED patients with SCI were included in this meta-analysis (Fig. 2). In GAQ1, the pooled results showed that sildenafil significantly improved erection compared with placebo in ED patients with SCI (OR = 5.96, 95% CI [3.36–10.55], $P < 0.00001$).

There were significantly higher successful sexual stimulation (P=0.008) and intercourse rates (P<0.001) in sildenafil group than placebo group [9].

According to the severity of SCI by ASIA grade (Fig. 4), the pooled results indicated that there was no statistical difference compared incomplete injury group with complete injury group(OR = 0.73, 95% CI [0.38–1.43], P=0.36).

Compared upper motor neuron (UMN) with lower motor neuron(LMN), there were better responsive rates in sildenafil (OR = 11.56, 95% CI [2.88–46.36], P=0.0006) (Fig. 5).

Because of incomplete data, we could not perform meta-analysis in IIEF scores, SEP and QOL.

3.2.1 Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias (Fig. 3). Egger's test was used to provide statistical evidence for funnel plot symmetry. In this meta-analysis, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry; the Egger's results did not show any evidence of publication bias.

3.3 Vardenafil

Giuliano et al. reported the efficacy of vardenafil, the results showed that after 12 weeks of treatment, mean per-patient penetration (76% vs 41%), maintenance (59% vs 22%), and ejaculation (19% vs 10%) success rates were significantly greater than placebo (all p<0.001).

3.3.1 Tadalafil

Giuliano et al. reported the efficacy of tadalafil, the results showed that after treatment, the tadalafil group compared with the placebo group was significantly greater (P<0.001) in mean per-patient percentage of successful penetration attempts (SEP question 2; 75.4% vs 41.1%) and intercourse attempts (SEP question 3; 47.6% vs 16.8%); percentage of improved erections (GAQ question 1; 84.6% vs 19.5%); and ejaculatory frequency (IIEF question 9; P=0.03).

Table 1. Baseline characteristics and quality of the included studies

PDE5Is	References, year	Study duration, weeks	Mean age, years patients/controls	Patients/controls	PDE5Is (dose, mg)	Outcome measures	Jadad score
Sildenafil	Maytom 1999	4 weeks	32/34	13/14	50mg	GAQ	3
	Hultling 2000 Giuliano 1999	6 weeks	38/38	89/89	25-100mg	IIEF-Q13、Q14、GAQ	2
	Ergin 2008	6 weeks	38.9/38.9	24/26	50-100mg	IIEF-15、GAQ、QOL	3
	Khorrami 2010	24 weeks	47.6/47.6	59/46	50-100mg	IIEF-5	3
Vardenafil	Giuliano 2006	12 weeks	40/39	207/211	5-20mg	IIEF-5、SEP-2、SEP-3、GAQ	3
Tadalafil	Giuliano 2007	12 weeks	37/39	142/44	10-20mg	IIEF-15、SEP、GAQ	3
Sildenafil vs Tadalafil	Popolo 2004	4 weeks	34.6/34.6	28/28	50mg vs 10mg	IIEF-5、IIEF-15、SEP-2、SEP-3	3

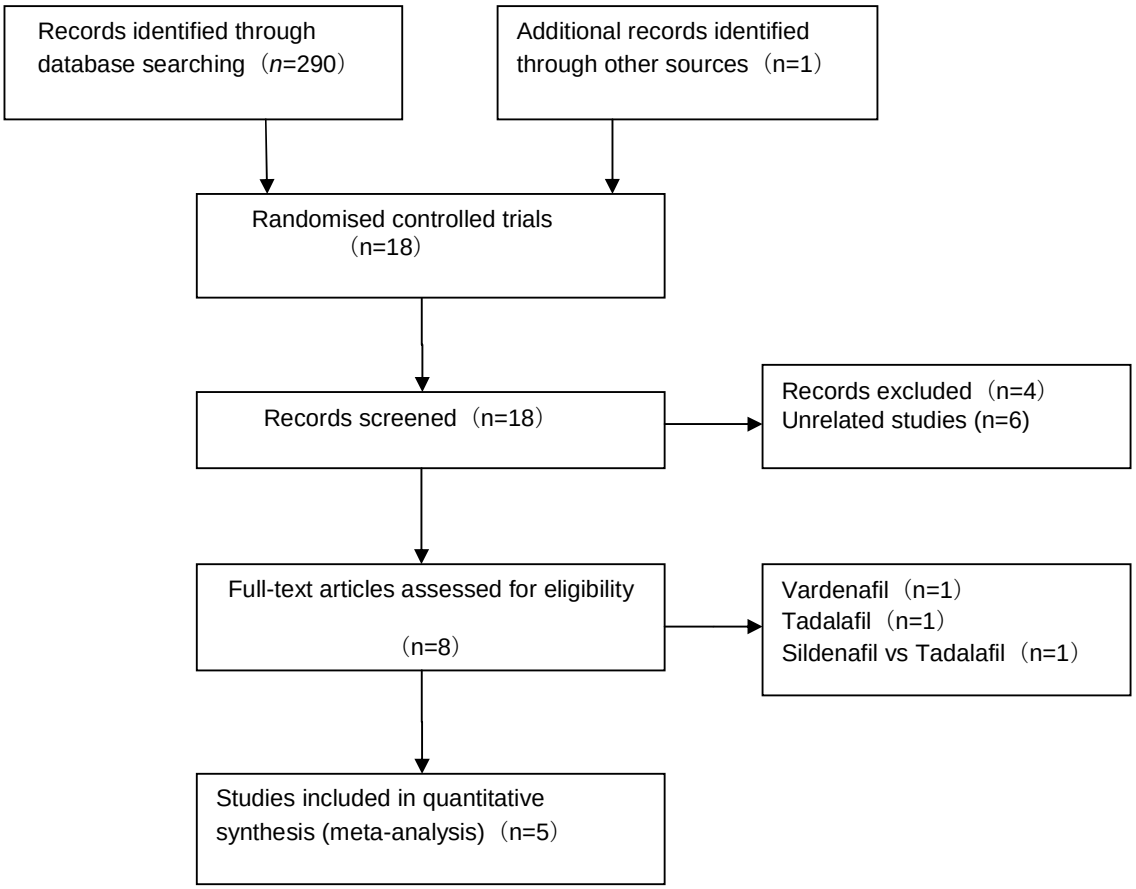

Fig. 1. Flow chart of meta-analysis

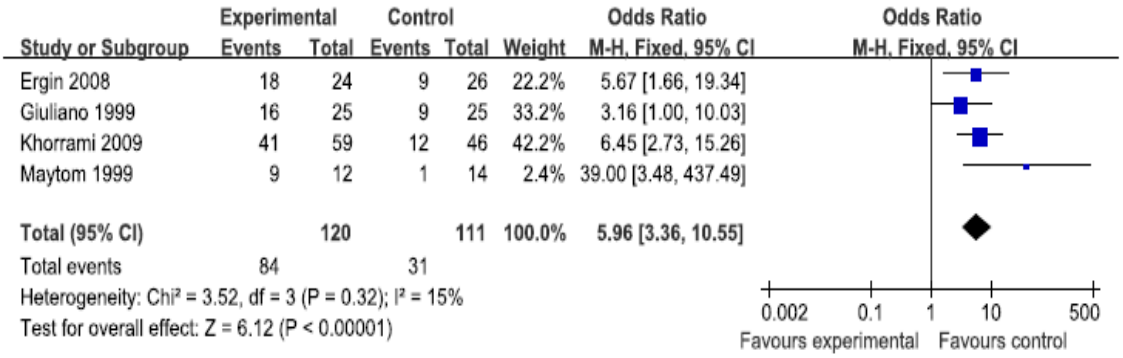

Fig. 2. Pooled results of the GAQ1 between Sildenafil and Placebo
CI=confidence interval

3.4 Sildenafil vs Tadalafil

Popolo et al. reported that tadalafil allowed a majority of men in this trial to achieve normal sexual functioning up to 24 h postdosing compared to sildenafil (P<0.01).

3.5 Adverse Events

The commonly reported AEs were headache (Tadalafil: 8.5%,12/142; Vardenafil: 15%,29/200; Sildenafil: 17%,42/247), flushing (Vardenafil: 6%,12/200; Sildenafil: 6.5%,16/247), gastro-

intestinal discomfort (Tadalafil: 2.1%,3/142; Vardenafil: 4%,7/200; Sildenafil: 4.5%,11/247), dizziness (Vardenafil: 2%,4/200; Sildenafil: 2%,5/247) and urinary tract infection (Tadalafil: 7.7%,11/142) in these studies. No severe adverse events were found.

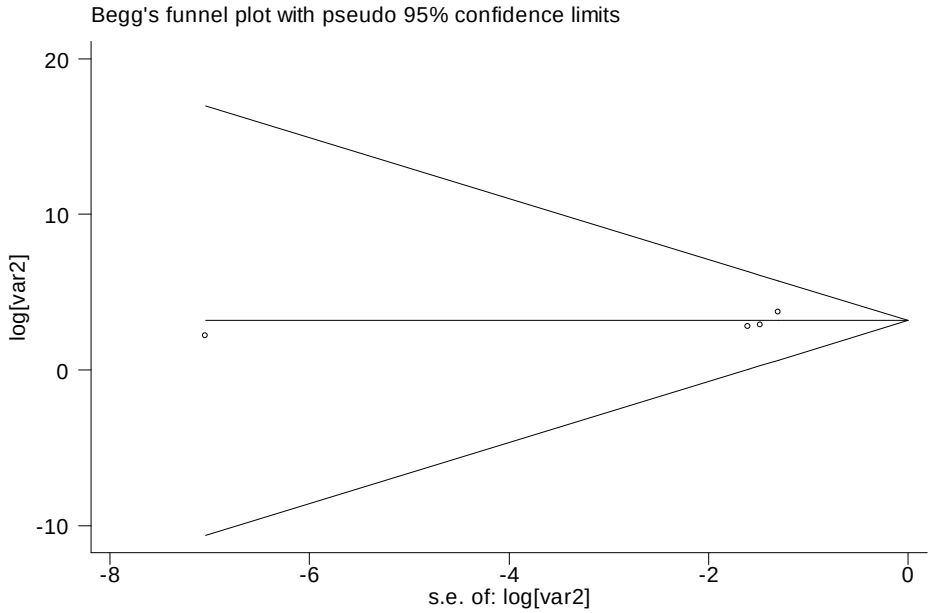

Fig. 3. Funnel plot of four randomised controlled trials which were included in meta-analysis

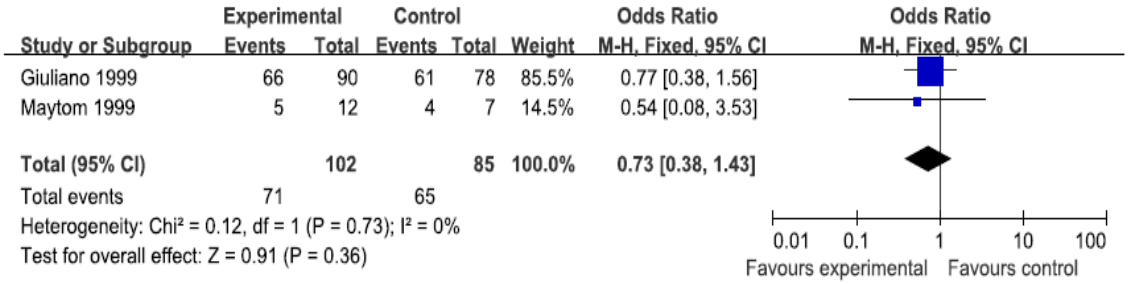

Fig. 4. Pooled results of the efficacy of Sildenafil on erectile dysfunction between incomplete injury group and complete injury group

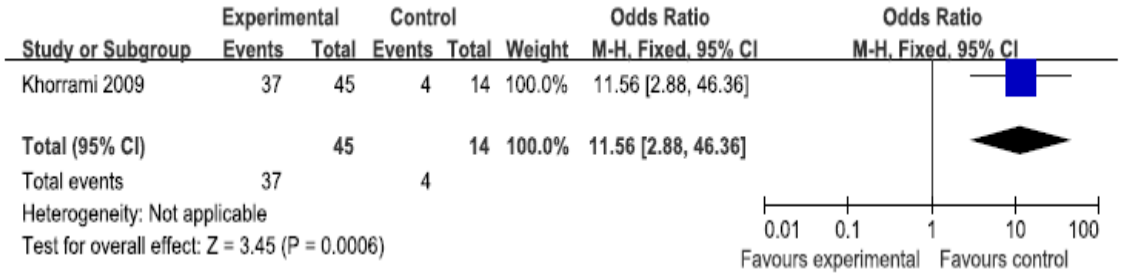

Fig. 5. Pooled results of the efficacy of Sildenafil on erectile dysfunction between upper motor neuron and lower motor neuron

4. DISCUSSION

Our systematic review found that PDE5 inhibitors were effective treatment in ED patients with SCI, especially for sildenafil. In sildenafil group, there was significantly erectile improvement, and it seems that the severity of spinal cord injury was not associated with the efficacy of sildenafil in ED patients with SCI. However, sildenafil can better improve sexual dysfunction in ED with UMN injury than LMN injury. In addition, although only one article studied the efficacy of vardenafil or tadalafil for ED patients with SCI, respectively, most patients felt improving erectile function. All patients were well-tolerated for PDE5 inhibitors treatment, no serious adverse effects were found, and the common adverse effects were headache, flushing, dizziness and urinary tract infection.

The previous review [29] indicated that after sildenafil treatment, the 94% of patients felt improving erections and had an ability to intercourse. Moreover, 72% of intercourse attempts were successful. Several non-RCTs also reported that vardenafil and tadalafil could be well-tolerated and improved erectile function in SCI patients [20,30]. This is consistent with our findings.

Erectile response rates were significantly higher in patients with incomplete SCI than complete SCI and in patients with UMN than LMN lesions [31]. Lombardi et al. [32] reported that the patients with UMN lesion had more therapeutic success rates of PDE5 inhibitors. However, our meta-analysis found that there was no statistical difference compared incomplete injury group with complete injury group except that there were better responsive rates in sildenafil compared UMN with LMN injuries.

Popolo et al. [27] conducted a RCTs including 28 patients with SCI, and found that patients felt more satisfactory with sex life compared tadalafil with sildenafil. Another non-RCT [20] compared the efficacy of different PDE5Is including sildenafil, vardenafil and tadalafil, the results showed that three PDE5Is were all effective and well-tolerated treatments for ED in SCI patients and sildenafil is more effective in treating ED. Apart from the above treatments, there are numerous therapeutic options for treating ED patients with SCI, including udenafil, mirodenafil, apomorphine, vacuum constriction devices, penile prostheses, and sacral neuromodulation now [33-39]. Because lack of data or RCTs, we could not perform meta-analysis to compare its difference. In future, it needs more high quality RCTs to clarify the results.

Our meta-analysis had some limitations. First, only the data of published studies were included in this meta-analysis. Unpublished studies tend to show more negative results. Second, because of the lack of the original data, we did not perform meta-analysis in IIEF scores, SEP and QOL. Third, the number of studies was relatively small for vardenafil and tadalafil, the results did not have enough statistical power for us to draw reliable conclusions. Fourth, lack of articles or data with other PDE5 inhibitors, such as udenafil and avanafil, so we were unable to assess effects of other PDE5 inhibitors for ED patients with SCI. Finally, because all included studies were low quality, we need more high quality RCTs to confirm these findings.

5. CONCLUSION

In summary, current evidence suggests that sildenafil is effective treatment for ED patients with SCI. No serious adverse events were found. In future, we need more high quality RCTs to confirm these findings and evaluate the effectiveness of other PDE5 inhibitors.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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