

# Efficacy and safety of short- and long-term, regular and on-demand regimens of phosphodiesterase type 5 inhibitors in treating erectile dysfunction after nerve-sparing radical prostatectomy: a systematic review and meta-analysis

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**Background:** We performed a meta-analysis to evaluate the efficacy and safety of short-term ( $\leq 6$  months) and long-term ( $> 6$  months), regular (OaD) and on-demand (PRN) regimens of phosphodiesterase type 5 inhibitors (PDE5-Is) in treating erectile dysfunction (ED) after nerve-sparing radical prostatectomy (NSRP).

**Methods:** We conducted a literature search in August 2016. Sources included PubMed, EMBASE, and MEDLINE databases. The main outcome was International Index of Erectile Function-Erectile Function (IIEF-EF) domain score, and the secondary outcome was treatment-emergent adverse events (TEAEs).

**Results:** Eight articles involving 13 randomized controlled trials (RCTs) were used in this analysis: they suggested that PDE5-Is can improve the IIEF-EF distinctly in comparison with placebo in short and long term (mean difference [MD]: 2.26, 95% confidence interval [CI]: 1.45–3.08,  $P < 0.00001$ , and MD: 4.5, 95% CI: 3.6–5.4,  $P < 0.00001$ ), and long-term use of PDE5-Is ( $> 6$  months) can improve the IIEF-EF distinctly in comparison with short-term use of PDE5-Is ( $\leq 6$  months) (MD: 3.9, 95% CI: 3.01–4.8,  $P < 0.00001$ ). OaD of PDE5-Is significantly improved the IIEF-EF compared to placebo in short and long term (MD: 4.08, 95% CI: 3.2–4.97,  $P < 0.00001$ , and MD: 4.74, 95% CI: 3.79–5.69,  $P < 0.00001$ ). No significant differences were found in IIEF-EF changes between PRN and placebo ( $\leq 6$  months) (MD: 2.64, 95% CI:  $-0.87$  to 6.14,  $P = 0.14$ ), and between PRN and OaD group ( $> 6$  months) (MD:  $-0.58$ , 95% CI:  $-9.86$  to 8.74,  $P = 0.91$ ). There were more TEAEs in PDE5-Is group in comparison with placebo (odds ratio [OR]: 1.55, 95% CI: 1.26–1.91,  $P < 0.0001$ ), and TEAEs in OaD group were not significantly different from those seen in PRN group (OR: 1.05, 95% CI: 0.78–1.4,  $P = 0.77$ ).

**Conclusion:** Our meta-analysis suggests that PDE5-Is are efficient and safe for treatment of ED after NSRP, and we should choose the regular regimen for short term and regular or on-demand regimen for long term. Further high-quality RCTs are needed to validate this result.

**Keywords:** erectile dysfunction, meta-analysis, nerve-sparing radical prostatectomy, phosphodiesterase type 5 inhibitors

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## Introduction

For clinically localized prostate cancer (PCa) in patients surviving through 10 years, nerve-sparing radical prostatectomy (NSRP) is a usual surgical treatment.<sup>1</sup>

Erectile dysfunction (ED) can be a relatively common sequela after radical prostatectomy (RP) for localized PCa,<sup>2-4</sup> despite the use of nerve-sparing techniques (NSRP). For ED after NSRP, many clinicians choose intracorporeal injections of alprostadil and vacuum pump therapy.<sup>5,6</sup> However, some questions remain on the effectiveness and safety of these treatments. In recent years, phosphodiesterase type 5 inhibitors (PDE5-Is) are considered to be the preferred treatment for ED.<sup>7</sup> However, the use of PDE5-Is for improving the ED after NSRP is still controversial, for example, the duration (short or long term) and regimen of treatment (regular or on-demand), and so it was necessary for us to perform a meta-analysis to evaluate the efficacy and safety of the administration of PDE5-Is for treating ED after NSRP.

The aim of our meta-analysis was to evaluate the efficacy and safety of short- and long-term, regular (OaD) and on-demand (PRN) regimens of PDE5-Is for treatment of ED after NSRP.

## Materials and methods

### Search strategy

We conducted a literature search in August 2016 using the PubMed, EMBASE, and MEDLINE databases. We scrutinized the references list of included studies to further choose more relevant articles and abstracts. We used the following search terms: erectile dysfunction, nerve-sparing radical prostatectomy, phosphodiesterase type 5 inhibitors, and randomised controlled trial.

### Inclusion criteria

Studies that met the following criteria were included: 1) They should be randomized controlled trials (RCTs) involving International Index of Erectile Function-Erectile Function (IIEF-EF) domain score: PDE5-Is versus placebo ( $\leq 6$  months), PDE5-Is versus placebo ( $> 6$  months), PDE5-Is ( $> 6$  months) versus PDE5-Is ( $\leq 6$  months), OaD versus placebo ( $\leq 6$  months), OaD versus placebo ( $> 6$  months), PRN versus placebo ( $\leq 6$  months), and OaD versus PRN ( $> 6$  months). 2) They should be RCTs involving adverse events: PDE5-Is versus placebo ( $> 6$  months) and OaD versus PRN ( $> 6$  months). 3) The outcome should have been reported as mean and standard deviation. 4) Full text of the study should be accessible.

### Trial selection

If the same group of subjects were studied by multiple experiments, each study was included. If the same study was published in different articles, the most frequently cited one

was included. We discussed each of the studies that were included or excluded. A flow diagram of the study selection process is presented in Figure 1.

## Quality assessment

Two independent reviewers assessed the quality of the included studies according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, including assessments of random sequence generation, allocation concealment, blinding methods, and description of withdrawals and dropouts.

## Data extraction

The data was extracted and cross-checked by two independent reviewers using a predesigned form, which included the first author's name, publication year, number of patients, age, country, interventions, and duration of therapy. The disagreements were discussed by a third person. The primary outcome was IIEF-EF domain score, and the secondary outcome was treatment-emergent adverse events (TEAEs).

## Statistical analysis

Statistical analysis was performed using Review Manager 5.1.0.<sup>8</sup> Outcomes expressed as continuous outcomes included mean difference (MD) and 95% confidence interval (CI), while  $P$ -value and odds ratio (OR) were used as dichotomous outcomes. We used  $I^2$  heterogeneity test to quantify the effect of the test results. If  $I^2$  was  $\leq 50\%$ , we chose a fixed-effects model, and if  $I^2$  was  $> 50\%$ , we chose a random-effects model. We used a funnel plot to evaluate the presence of publication bias. Funnel plot of the studies represented in this meta-analysis is presented in Figure 2.

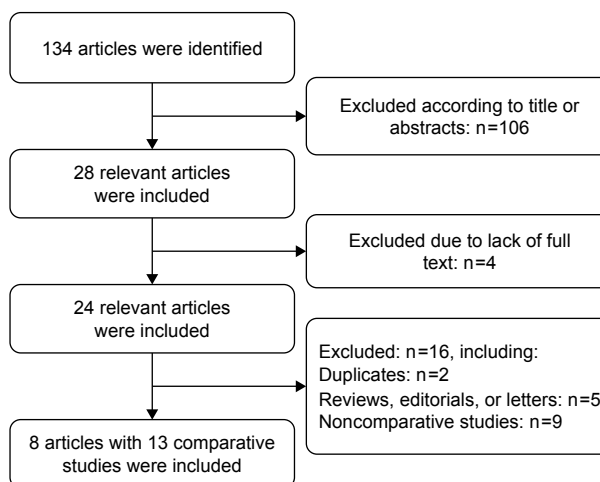
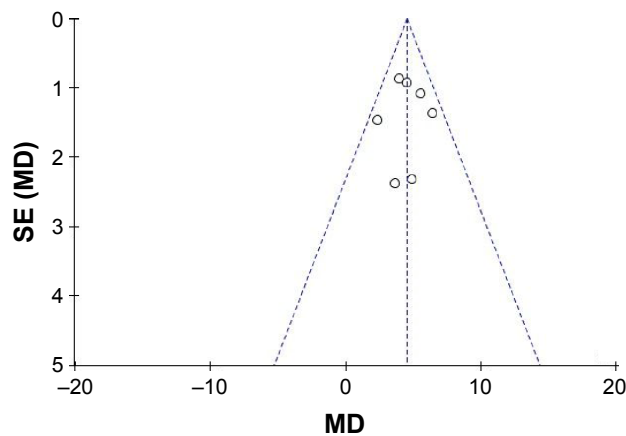


Figure 1 A flow diagram of the study selection process.



**Figure 2** Funnel plot of the studies represented in this meta-analysis.  
**Abbreviations:** MD, mean difference; SE, standard error.

## Results

### Characteristics of the individual studies

Eight articles involving 13 studies and 1,806 patients were finally found eligible for this meta-analysis.<sup>9–16</sup> Five RCTs compared PDE5-Is with placebo over the short term ( $\leq 6$  months), seven RCTs compared PDE5-Is with placebo over the long term ( $> 6$  months), and one RCT compared on-demand sildenafil 50 mg nightly and on-demand sildenafil 50 mg over the long term ( $> 6$  months). Randomization sequencing and outcome data reporting were deemed mostly adequate. Allocation concealment, and withdrawals and drop-outs were poorly reported. The main characteristics and quality assessment of the eligible studies are presented in Table 1.

### Efficacy

#### IIEF-EF domain score

Five RCTs over the short term ( $\leq 6$  months), representing 286 participants (137 in the placebo group and 149 in the PDE5-Is group), included data about IIEF-EF domain score changes. Heterogeneity test showed no heterogeneity among the trials, and so we chose a fixed-effects model. The results showed that PDE5-Is can improve the IIEF-EF distinctly in comparison with placebo in short term ( $\leq 6$  months). The pooled estimate of MD was 2.26, and the 95% CI was 1.45–3.08 ( $P < 0.00001$ ; Figure 3A).

Seven RCTs over the long term ( $> 6$  months), representing 387 participants (187 in the placebo group and 200 in the PDE5-Is group), included data about IIEF-EF domain score changes. Heterogeneity test showed no heterogeneity among the trials, and so we chose a fixed-effects model. The results showed that PDE5-Is can improve the IIEF-EF distinctly in comparison with placebo in long term ( $> 6$  months). The pooled estimate of MD was 4.5, and the 95% CI was 3.6–5.4 ( $P < 0.00001$ ; Figure 3B).

Five RCTs compared the short-term ( $\leq 6$  months) regimen of PDE5-Is with the long-term ( $> 6$  months) regimen, representing 298 participants (149 in the short-term group and 149 in the long-term group), and included data on IIEF-EF domain score changes. Heterogeneity test showed no heterogeneity among the trials, and so we chose a fixed-effects model. The results showed that long-term use of PDE5-Is ( $> 6$  months) can improve the IIEF-EF distinctly in comparison with short-term use of PDE5-Is ( $\leq 6$  months). The pooled estimate of MD was 3.9, and the 95% CI was 3.01–4.8 ( $P < 0.00001$ ; Figure 3C).

By dividing the included studies into on-demand (PRN) and regular (OaD) regimen studies, we found that regular (OaD) regimen of PDE5-Is significantly improved the IIEF-EF domain score compared to placebo in short and long term (MD: 4.08, 95% CI: 3.2–4.97,  $P < 0.00001$ , and MD: 4.74, 95% CI: 3.79–5.69,  $P < 0.00001$ ) (Figure 4A and B). Two RCTs compared on-demand (PRN) group with placebo with respect to short-term use ( $\leq 6$  months), and no significant differences were found in IIEF-EF domain score changes between the both groups (MD: 2.64, 95% CI: –0.87 to 6.14,  $P = 0.14$ ) (Figure 4C). Also, two RCTs compared on-demand (PRN) group with regular (OaD) regimen group with respect to long-term use ( $> 6$  months), representing 178 participants (90 in the on-demand group and 88 in the regular regimen group), and included data on IIEF-EF domain score changes. No significant differences were found in IIEF-EF domain score changes between the two groups (MD: –0.58, 95% CI: –9.86 to 8.74,  $P = 0.91$ ) (Figure 4D).

### Safety assessments: TEAEs

On the whole, the incidence rate of TEAEs in PDE5-Is and placebo groups was 59.63% and 48.37%, respectively. Headache, flushing, dyspepsia, and rhinitis were some of the most common adverse events, all of which were not severe. The results showed that PDE5-Is group had more TEAEs than the placebo group (OR: 1.55, 95% CI: 1.26–1.91,  $P < 0.0001$ ; Figure 5A). Also, three RCTs compared regular (OaD) regimen with on-demand (PRN) regimen in terms of TEAEs. Heterogeneity test showed no heterogeneity among the trials, and so we chose a fixed-effects model, and we made the OR as the effect size for meta-analysis (OR: 1.05, 95% CI: 0.78–1.4,  $P = 0.77$ ; Figure 5B). TEAEs in regular regimen group were not significantly different from those in on-demand group.

## Discussion

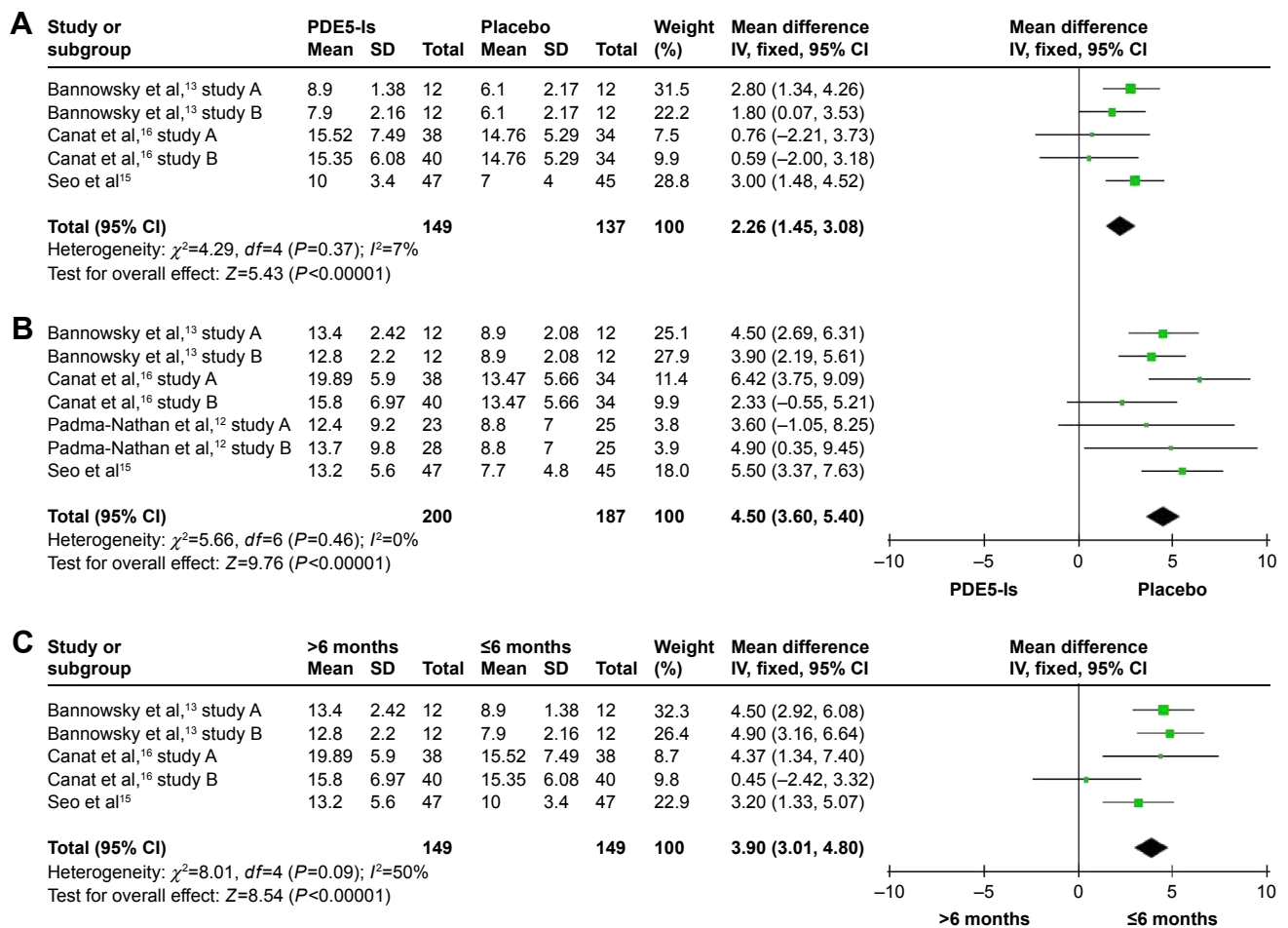
PCa is the one of the most common malignant tumors in men, and many patients with PCa are treated with RP every year

**Table 1** The main characteristics and quality assessment of eligible studies

Studies	Therapy in experimental group	Therapy in control group	Dosing of experimental group	Age (median)	Country	Simple size		Inclusion criteria	Duration of therapy (months)	Quality assessment <sup>a</sup>
						Experimental	Control			
Bannowsky et al, <sup>13</sup> study A	Vardenafil	Placebo	5 mg/day	61.4	Germany	12	12	Men with ED after NSRP, who had been sexually active before surgery	3, 6, 12	B
Bannowsky et al, <sup>13</sup> study B			10 mg/day			12				B
Canat et al, <sup>16</sup> study A	Tadalafil	Placebo	20 mg/day	62.63	Turkey	38	34	Men with ED after retropubic bilateral NSRP, 2 weeks after surgery	1.5, 12	A
Canat et al, <sup>16</sup> study B			20 mg on demand			40				A
Padma-Nathan et al, <sup>12</sup> study A	Sildenafil	Placebo	50 mg/day	55	America, Canada, Belgium, France, Australia	40	42	Men with ED after NSRP, 4 weeks after surgery	9	A
Padma-Nathan et al, <sup>12</sup> study B			100 mg/day			41				A
Seo et al <sup>15</sup>	Tadalafil	Placebo	5 mg/day	67.9	Korea	47	45	Men with ED after NSRP	6, 12	A
Montorsi et al <sup>9</sup>	Tadalafil	Placebo	20 mg on demand	59.8	Italy, America, Canada	102	201	Men with ED following bilateral NSRP	3	A
Montorsi et al, <sup>10</sup> study A	Vardenafil	Placebo	10 mg/day	57.4	Italy, America, Canada, Belgium, Germany	207	206	Men with ED undergo bilateral NSRP within 1 month, who had been sexually active before surgery	9	A
Montorsi et al, <sup>10</sup> study B			10 mg on demand			204				
Montorsi et al, <sup>11</sup> study A	Tadalafil	Placebo	5 mg/day	58.6	Italy, America, Canada, Spain, Germany	139	141	Men <68 years of age at the time of NSRP, with ED after NSRP, who had been sexually active before surgery	9	A
Montorsi et al, <sup>11</sup> study B			20 mg on demand			143				
Pavlovich et al <sup>14</sup>	Sildenafil	Sildenafil	50 mg nightly	54	America	50	50	Age <65 years, no PDE5 inhibitor use, and presence of a steady sexual partner, with at least one neurovascular bundle preserved	13	A

**Notes:** <sup>a</sup>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 were only partially met or were unclear, the study was deemed to have a moderate risk of bias.

**Abbreviations:** ED, erectile dysfunction; NSRP, nerve-sparing radical prostatectomy; PDE5, phosphodiesterase type 5.



**Figure 3** Forest plots showing changes in the IIEF-EF domain score: (A) PDE5-Is versus placebo ( $\leq 6$  months), (B) PDE5-Is versus placebo ( $> 6$  months), and (C) PDE5-Is ( $> 6$  months) versus PDE5-Is ( $\leq 6$  months).

**Abbreviations:** IIEF-EF, International Index of Erectile Function-Erectile Function; PDE5-Is, phosphodiesterase type 5 inhibitors; SD, standard deviation; CI, confidence interval.

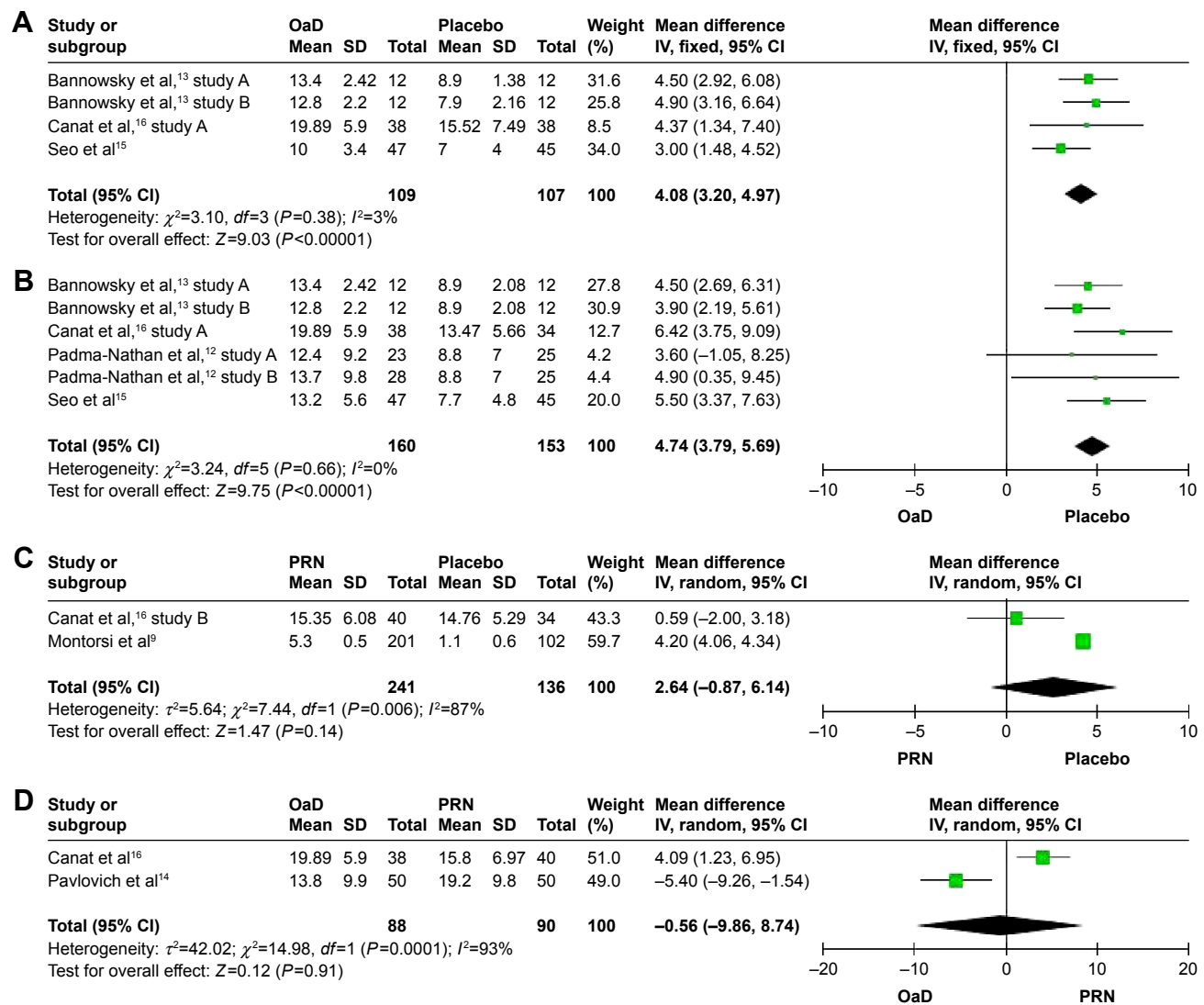
worldwide. ED is still a frequent complication among men undergoing RP, though the procedure is nerve sparing. The rate of occurrence of complete ED has been reported to be 26%–100%, and partial ED, 16%–48%.<sup>17</sup> Lately, PDE5-Is are considered to be the best choice for ED.<sup>7</sup>

PDE5-Is have an influence on nitric oxide cyclic guanosine monophosphate (cGMP) pathway by degrading cGMP, which is the dominating presentation of phosphodiesterase in male corpus cavernosum.<sup>18</sup> When neurologic injury happens, penile hypoxia and fibrosis result in the lack of spontaneous nocturnal erections, which reduces the release of nitric oxide.<sup>19,20</sup> The reduction in nitric oxide production results in a decrease in the amount of available cGMP. PDE5 can be inhibited by PDE5-Is, and as a result, cGMP can be metabolized more which will lead to a promotion in cGMP levels.<sup>21</sup> This promotion of the level of cGMP combined with nitric oxide production leads to corporal smooth muscle relaxation, and this makes the penis congestive and results in erection.<sup>22,23</sup>

Because nerve has an important role in the whole process, we consider about the use of PDE5-Is in treatment of ED after NSRP in our study.

PDE5-Is can be administered for short or long term, and regularly or on demand. There are many studies that proved that PDE5-Is are effective in treatment of ED after NSRP. However, the efficacy of PDE5-Is is still controversial, and it is difficult to decide the best treatment strategy. Also, there is no agreement on the mode of administration of PDE5-Is. So, in our study, we assessed the effect of duration (short term and long term) and strategy of treatment (regular and on demand) to evaluate the efficacy of PDE5-Is in treatment of ED after NSRP.

From the results of our study, we found that PDE5-Is are effective in treating ED after NSRP in short term and long term. Also, by comparing short- and long-term regimens, we found that PDE5-Is could lead to a significant improvement in the IIEF-EF domain score when they are used for a long term.



**Figure 4** Forest plots showing changes in the IIEF-EF domain score: (A) OaD versus placebo ( $\leq 6$  months), (B) OaD versus placebo ( $> 6$  months), (C) PRN versus placebo ( $\leq 6$  months), and (D) OaD versus PRN ( $> 6$  months). OaD and PRN represent regular and on-demand regimens of PDE5-Is.

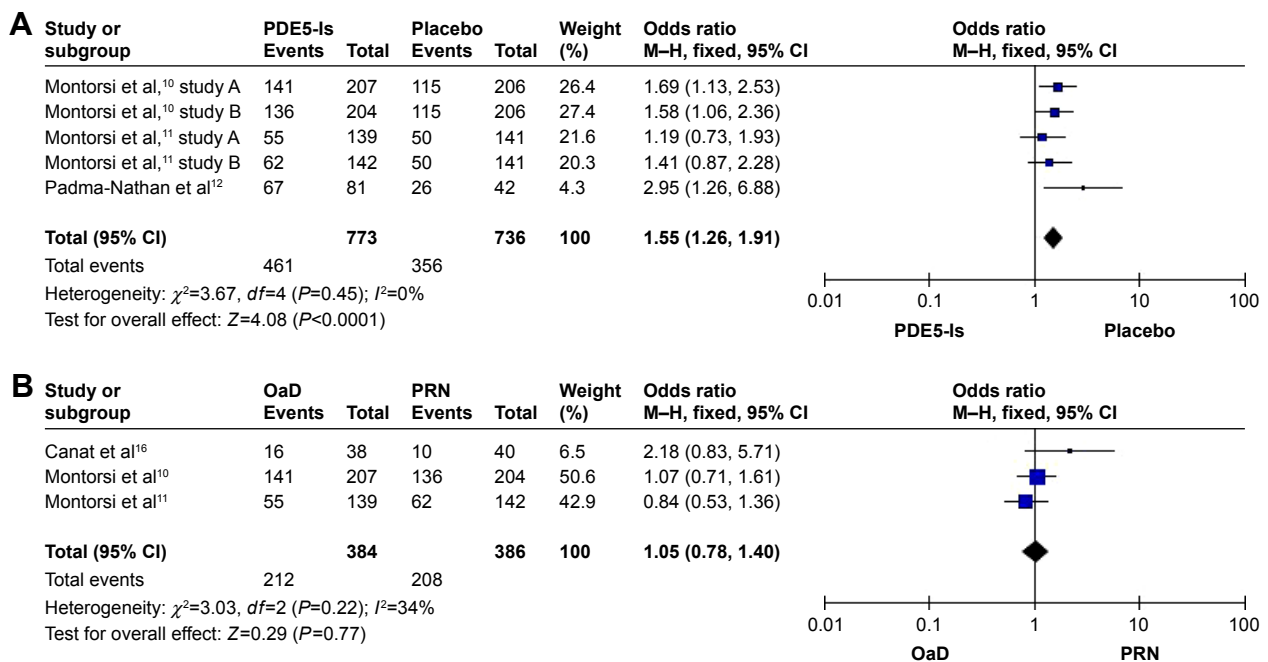
**Abbreviations:** IIEF-EF, International Index of Erectile Function-Erectile Function; PDE5-Is, phosphodiesterase type 5 inhibitors; SD, standard deviation; CI, confidence interval.

Taking strategy of treatment (regular and on demand) into account, our analysis found that regular regimen of PDE5-Is can improve the IIEF-EF domain score compared to placebo in the short term but on-demand regimen of PDE5-Is could not. So, our study suggests that we should choose regular regimen of PDE5-Is for short term. From the results of long-term use, we found that regular regimen of PDE5-Is can improve the IIEF-EF domain score compared to placebo, but the data on comparison of on-demand regimen of PDE5-Is with placebo is lacking. However, two RCTs<sup>14,16</sup> have compared long-term regular regimen with long-term on-demand regimen of PDE5-Is in terms of the IIEF-EF domain score and found no significant difference between the two groups. So, we indirectly conclude that on-demand regimen of PDE5-Is

can also improve the IIEF-EF domain score compared to placebo. Thus, our study suggests that we could choose regular or on-demand regimen for long term.

The safety results of our meta-analysis showed that headache, flushing, dyspepsia, and rhinitis were some of the most common adverse events, all of which were not severe. There were more TEAEs in PDE5-Is group than in the placebo group for the long-term use, but TEAEs in regular regimen group were not significantly different from those in on-demand regimen group.

To summarize, our results showed that PDE5-Is can improve the erectile function distinctly in patients with ED after NSRP. Particularly, from the analysis of our study, we suggest that we should choose regular regimen of PDE5-Is



**Figure 5** Forest plots showing changes in adverse events: (A) PDE5-Is versus placebo (>6 months) and (B) OaD versus PRN (>6 months). OaD and PRN represent regular and on-demand regimens of PDE5-Is.

**Abbreviations:** PDE5-Is, phosphodiesterase type 5 inhibitors; CI, confidence interval.

for short term, and for the long term, both regular and on-demand regimens could be considered. Also, TEAEs will not be significantly different between the long-term regular and on-demand regimens.

The limitations of this meta-analysis are as follows: 1) The data on long-term on-demand regimen of PDE5-Is is lacking. 2) The RCTs comparing long-term regular and on-demand regimens are not sufficient. 3) Regarding safety, there is no sufficient data about the TEAEs for the short-term use of PDE5-Is. Further high-quality RCTs are needed to evaluate the efficacy and safety of PDE5-Is in treating ED after NSRP.

## Conclusion

Our meta-analysis suggests that PDE5-Is are efficient and safe for treatment of ED after NSRP, and we should choose regular regimen for short term and regular or on-demand regimen for long term. Further high-quality RCTs are needed to validate this result.

## Disclosure

The authors report no conflicts of interest in this work.

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