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Efficacy and Safety of Combination Comprising Tamsulosin and PDE5-Is, Relative to Monotherapies, in Treating Lower Urinary Tract Symptoms and Erectile Dysfunction Associated With Benign Prostatic Hyperplasia: A Meta-Analysis

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Abstract

We report safety and efficacy of a combination therapy, comprising tamsulosin and phosphodiesterase type 5 inhibitors (PDE5-Is), relative to monotherapy, to ascertain its potential in treating lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) secondary to benign prostatic hyperplasia (BPH) after 3 months' treatment. We screened MEDLINE, EMBASE, and the Cochrane Controlled Trials Register databases, for randomized controlled trials, and obtained eight articles comprising 1144 participants. Results showed that the combination group had superior outcomes with regard to International Prostate Symptom Score (IPSS) and Qmax, compared to the other two groups. The combination group also had superior efficacy with regard to International Index of Erectile Function (IIEF) than the tamsulosin group, but not over the PDE5-Is group. Further, the combination group showed better efficacy in IPSS voiding and quality of life (QoL) compared to the PDE5-Is group. An analysis of safety outcomes revealed extremely high adverse events (AEs) and pain in the combination group. However, therapy discontinuation due to pain and AEs did not increase with increase in AEs. Overall, our findings indicate that a combination of tamsulosin and PDE5-Is is superior to individual tamsulosin and PDE5-Is monotherapy, with regard to improving LUTS and ED secondary to BPH.

Keywords

quality of life, general health and wellness, sexual health, sexuality, sexual dysfunction, sexuality, sexual disorders, sexuality

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Benign prostatic hyperplasia (BPH), distinguished by hyperplasia of smooth muscles and epithelial cells in the transitional part of prostate, is one of the most popular geriatric diseases, whose incidence rises with age (Laumann et al., 2007; Olesovsky & Kapoor, 2016; Zhang & Park, 2015). Generally, BPH clinically manifests as lower urinary tract symptoms (LUTS), mainly nocturia, urine flow interruption, and susceptibility to acute urinary retention (AUR), among others. In addition, the disease is also associated with erectile dysfunction (ED) and ejaculatory dysfunction (Anderson et al., 2001; Rosen, 2006; Vallancien et al., 2003). Previous studies

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have reported a strong correlation between severe LUTS and ED (El-Sakka, 2006). Based on this, we will focus on ED-related clinical therapies during LUTS treatment. Alpha-1 adrenoceptor antagonists (represented by tamsulosin) represents the first-line drug used for managing BPH-related LUTS, with its role management of ED also being explored (Hofner et al., 1999). Previous research has applied phosphodiesterase type 5 inhibitors (PDE5-Is; represented by tadalafil, sildenafil, vardenafil), for ED management, and reported their efficacy in relieving BPH-related LUTS (Andersson et al., 2011; Chapple et al., 2015). A combination of tamsulosin and PDE5-Is has also been tested, owing to their complementary action during treatment of LUTS and ED. This therapy has gained considerable attention.

To date, three meta-analyses have demonstrated the efficacy of tamsulosin or PDE5-Is alone in alleviating LUTS and ED (Laydner et al., 2011; Liu et al., 2011; Zhang et al., 2019). However, only one has described the efficacy of a combination therapy (Zhou et al., 2019). Furthermore, several discrepancies are evident regarding the number of randomized controlled trials (RCTs) included as well as analysis of outcome indicators. One of the reasons may be language barrier, since restrictions on the English language may hamper adequate interpretation of results. Therefore, we sought to comprehensively evaluate the efficacy and safety of a combined therapy comprising tamsulosin and PDE5-Is, relative to respective monotherapies, for treatment of BPH-related LUTS and ED after 3 months' treatment using a meta-analysis.

Materials and Methods

Search Strategy

We adopted the Preferred Reporting Items of the System Review and Meta-analysis (PRISMA) list for this meta-analysis (Moher et al., 2010). Summarily, two authors independently searched for and reviewed all RCTs describing the association between combination therapy with tamsulosin and PDE5-Is, as well as their respective monotherapies, from inception until May 1, 2020. Searches were performed on MEDLINE, EMBASE, and the Cochrane Controlled Trials Register databases, using various Medical Subject Headings (MeSH) terms. These included "tamsulosin," "PDE5-Is," "ED," "BPH," "LUTS," and "RCTs." The researchers were not restricted by language and excluded repeated studies. In case of disputes, a third person was called upon for consensus.

Inclusion Criteria and Article Selection

Articles on RCTs that met the following criteria were retrieved: (a) described a combination therapy comprising tamsulosin and PDE5-Is versus tamsulosin alone or PDE5-Is for treatment of ED and LUTS secondary to BPH (BPH-LUTS); (b) data associated with these parameters and full-text content were available; (c) authentic data chiefly covering the sum of subjects and the meritorious consequences of each index can be obtained; and (d) trials that turned out to be RCTs. We also included updated findings following the publication of associated outcomes in various magazines or issues at diverse times. Only studies that reported participation by an identical body of patients in numerous experiments were included. A flowchart describing PRISMA selection is shown in Figure 1.

Quality Assessment

We applied both the Cochrane bias risk evaluation facility and the Jadad scale for assessment of the methodological quality of all RCTs (Cumpston et al., 2019; Jadad et al., 1996). Each RCT was classified based on the following quality assessment criteria: (a) had low potential of bias for meeting almost all the quality criteria; (b) considered a secondary probability for fulfilling partial quality criteria or indistinct; or (c) had a high possibility of bias for conforming to bare quality criteria. All reviewers independently evaluated the quality of the studies and disagreements were settled by discussions.

Data Extraction

The two reviewers independently extracted data using a predefined data extraction tabulation method. The extracted data included: (a) first author's name; (b) country of study; (c) median age of the patients; (d) treatment therapy; (e) sample size in each group; (f) treatment duration; (g) main inclusion population; (h) outcome measures; (i) number of adverse events (AEs); and (j) discontinuation due to pain, including myalgia, back pain, headache, and bone pain as well as AEs. Clinically significant data can produce measurable results for participants. This study did not require ethical approval since it was a review of published research.

Statistical Analysis

Data were analyzed using Review Manager version 5.3.0 (Cochrane Collaboration, Oxford, UK). We applied fixed or random effect models to assess indicators and mean difference (*MD*) for the analysis and interpretation of continuous data. Dichotomous outcomes were presented as odds ratios (*OR*) at 95% confidence interval (CI). Providing analysis showed that the p value was greater than .05, the study was considered homogeneous, and a fixed effect model was applied in the study. Heterogeneity in the results was evaluated using the I-square (I^2) test. A random effect model was adopted in cases where an I^2 value was greater than 50%. Sources of heterogeneity were analyzed using

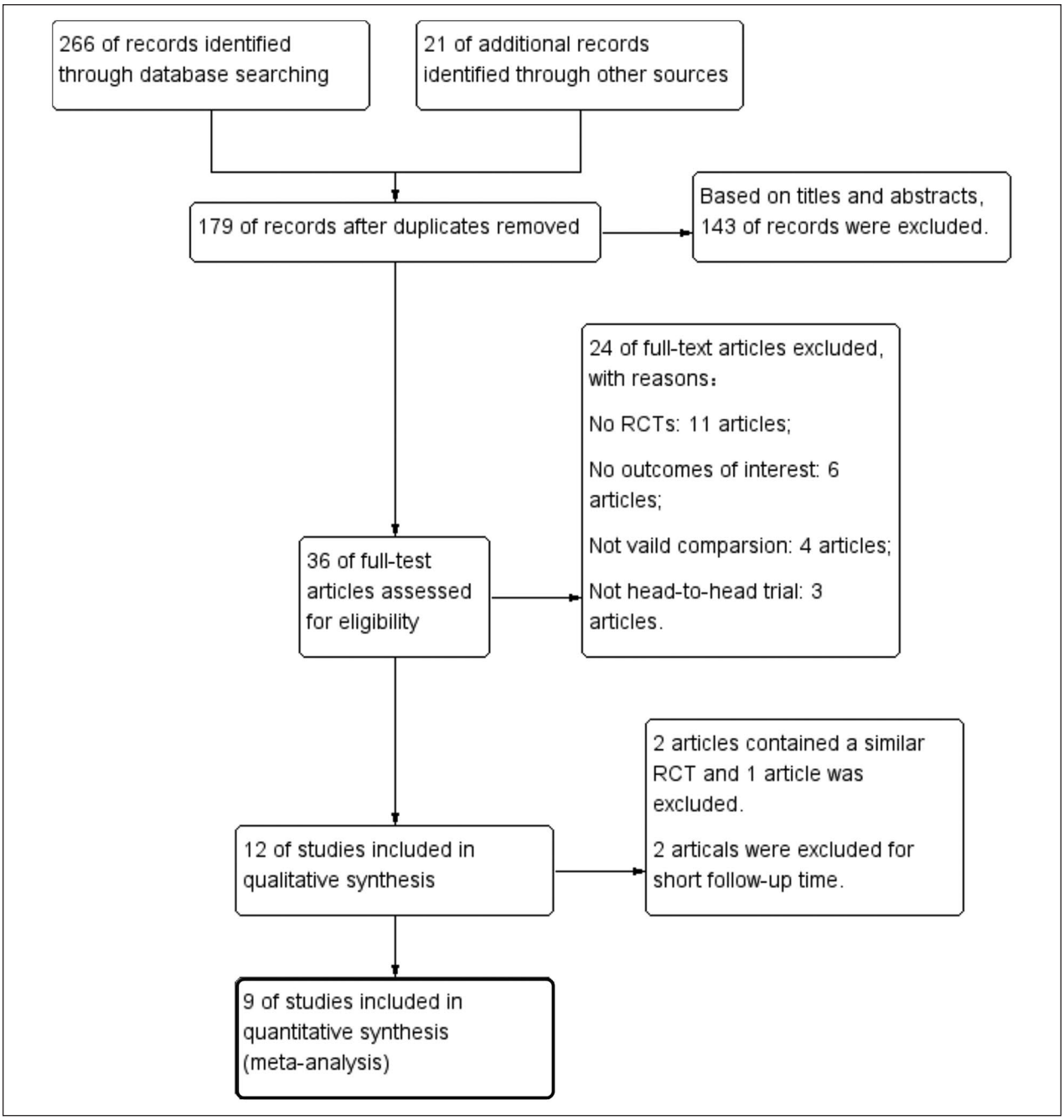

Figure 1. Flowchart of the study selection process. RCTs = randomized controlled trials.

subgroup or sensitivity analyses. Data followed by $p < .05$ were considered statistically significant.

Results

Study Selection, Search Results, and Characteristics of the Trials

Searching the aforementioned databases and other sources resulted in 287 articles. Two hundred and fifty-one articles were excluded following screening of abstracts and titles as well as removal of duplicate articles. An additional 25, of the remaining 36 articles, lacked the relevant data and were therefore excluded (details in Figure 1). The two reviewers independently rated the papers based on our inclusion criteria. Finally, eight RCTs (Bechara et al., 2008; Dell'Atti & Cuneo, 2013; Fawzi et al., 2017; Karami et al., 2016; Kim et al., 2017; Nagasubramanian et al., 2020; Sebastianelli et al., 2019; Singh et al., 2014) were included in our analysis and used

to evaluate the efficacy and safety of a combined therapy comprising tamsulosin and PDE5-Is, relative to respective monotherapies for treatment of LUTS and ED associated with BPH. Characteristics of these studies are outlined in Table 1.

Risk of Bias in Trials

All included studies were RCTs, with specific randomized protocols. Quality assessment outcomes are shown in Table 1, whereas a summary of risk of bias is shown in Figure 2. Bias mainly resulted from differences in dose of tamsulosin and PDE5-Is. The analysis of bias in the articles resulted in highly symmetrical plots, comprising six squares in articles evaluating efficacy of tamsulosin and PDE5-Is in combination with tamsulosin alone in the treatment of LUTS and ED (Figure 3a), whereas five squares represented bias in articles describing tamsulosin and PDE5-Is in combination with PDE5-Is alone (Figure 3b). These results showed no evidence of bias among the included articles.

Efficacy

Total IPSS

The IPSS from six RCTs comprising 605 patients (297 in combination group, 308 in tamsulosin group) showed that the combination group exhibited a significant decline ($MD = -2.27$; 95% CI [−2.82, −1.63]; $p < .00001$) compared with the tamsulosin group (Figure 4a). In addition, total IPSS from five RCTs comprising 694 patients (354 in the combination and 340 in the PDE5-Is group) revealed a marked decline in the combination, relative to the PDE5-Is group, ($MD = -3.03$; 95% CI [−4.28, −1.77]; $p < .00001$; Figure 5a).

IPSS Storage

Three RCTs using 506 patients (261 and 245 in the combination and PDE5-Is groups, respectively) resulted in $MD = -0.66$ and 95% CI [−1.42, 0.10], $p = .09$; Figure 5b. These results indicated that the combination therapy had superior efficacy compared to PDE5-Is in IPSS storage.

IPSS Voiding

Three articles containing 506 patients (261 and 245 in the combination and PDE5-Is groups, respectively) showed improvement of IPSS voiding ($MD = -0.98$; 95% CI [–1.50, –0.47], $p = .0002$; Figure 5c). These outcomes indicated that the combination therapy had superior efficacy compared to PDE5-Is in IPSS voiding.

Qmax

Five RCTs comprising 574 participants (283 and 291 in the combination and tamsulosin groups, respectively) had data on maximum flow rate (Qmax). The cumulative estimates revealed $MD = 0.88$ (95% CI [0.18, 1.58], $p = .01$; Figure 4b). Another five RCTs, comprising 694 participants (354 and 340 in the combination and PDE5-Is groups, respectively) reported Qmax data with a cumulative estimate of $MD = 1.51$ and 95% CI [0.97, 2.04], $p < .00001$; Figure 5d. From these studies, it was evident that the combination therapy was more superior in ameliorating Qmax, relative to tamsulosin and PDE5-Is.

QoL

Three RCTs comprising 326 patients (162 and 164 in the combination and tamsulosin groups, respectively) described improvement of quality of life (QoL). Forest plots revealed $MD = -0.33$ and 95% CI [–0.83, –0.17], $p = .19$; Figure 4c. On the other hand, four RCTs compared QoL in 578 patients (296 and 282 in the combination and PDE5-Is groups, respectively). Forest plots for this case revealed $MD = -0.33$ and 95% CI [–0.47, –0.19]; $p < .00001$; Figure 5e). Overall, these findings indicated that the combination therapy is significantly superior to PDE5-Is in improving QoL, but not better than tamsulosin.

PVR

Changes in post-void residual (PVR) urine volumes were also reported. Forest plots for four RCTs comprising 443 patients (220 and 223 in the combination and tamsulosin groups, respectively) revealed $MD = -5.10$ and 95% CI [–11.08, 0.87], $p = .09$; Figure 4d, whereas those for four RCTs with 619 patients (304 and 315 in the combination and PDE5-Is groups, respectively) resulted in $MD = -4.05$ and 95% CI [–12.50, 4.40], $p = .35$; Figure 5f. These findings indicated that the combination therapy was not significantly superior to tamsulosin and PDE5-Is with regard to influencing PVR.

IIEF

In four RCTs comprising 443 patients (220 and 223 in the combination and tamsulosin groups, respectively), it was evident that patients treated with combination therapy had a better reaction than those under monotherapy ($MD = 2.75$, 95% CI [1.77, 3.73], $p < .00001$; Figure 4e). However, data from five RCTs comprising 694 patients (250 and 252 in the combination and PDE5-Is groups, respectively) showed that the combination therapy did not significantly affect reaction compared to PDE5-Is

Table 1. Details of the Included Studies.

Study	Country	Age (Median)	Therapy With Combination Group	Therapy With Tamsulosin Alone Group	Therapy With PDE5-Is Alone Group	Sample Size			Treatment Duration	Main Inclusion Population	Outcome Measures	Quality Assessment
						Combination Group	Tamsulosin Alone Group	PDE5-Is Alone Group				
Bechara et al., 2008	Argentina	63.7	Tamsulosin 0.4 mg/day plus tadalafil 20 mg/day	Tamsulosin 0.4 mg/day plus daily placebo	Unset	14	13	Unset	90 days	Men ≥50 years of age with a history of LUTS secondary to BPH, IPSS ≥12, tPSA ≤4.0 ng/mL, Qmax > 5 mL/s and <15 mL/s, MVV > 125 mL	IPSS, QoL index, VAS, GAQ, Qmax, PVR, IIEF	Low risk
Dell'Atti and Cuneo, 2013	Italy	63.8	Tamsulosin 0.4 mg/day plus tadalafil 5 mg/day	Tamsulosin 0.4 mg/day	Tadalafil 5 mg/day	49	48	51	3 months	Men ≥50 years of age with a history of ED and BPH, IPSS ≥8, PSA ≤2.5 ng/mL, Qmax > 5 mL/s and <15 mL/s, PVR < 120 mL, IIEF ≥11, PV ≤40 mL.	Total IPSS, QoL, Qmax, PVR, IIEF-5	Low risk
Singh et al., 2014	India	61.6	Tamsulosin 0.4 mg/day plus tadalafil 10 mg/day	Tamsulosin 0.4 mg/day	Tadalafil 10 mg/day	44	45	44	3 months	Men ≥45 years of age with a history of LUTS secondary to BPH, IPSS > 8, Qmax > 5 mL/s and < 15 mL/s, PSA ≤4.0 ng/mL, MVV > 125 mL.	IPSS, QoL, Qmax, PVR, IIEF	Low risk
Karami et al., 2016	Iran	68.4	Tamsulosin 0.4 mg/day plus tadalafil 20 mg/day	Tamsulosin 0.4 mg/day	Tadalafil 20 mg/day	58	59	58	3 months	Men ≥45 years of age, IPSS ≥12, and having a history of ED.	IPSS, Qmax, PVR, IIEF, IPSS storage, IPSS voiding	Low risk

(continued)

Table 1. (continued)

Study	Country	Age (Median)	Therapy With Combination Group	Therapy With Tamsulosin Alone Group	Therapy With PDE5-Is Alone Group	Sample Size			Treatment Duration	Main Inclusion Population	Outcome Measures	Quality Assessment
						Combination Group	Tamsulosin Alone Group	PDE5-Is Alone Group				
Fawzi et al., 2017	Egypt	66.0	Tamsulosin 0.4 mg/day plus sildenafil 25 mg/day	Tamsulosin 0.4 mg/day plus daily placebo	Unset	63	68	Unset	3 months	Men with LUTS or BPH without medical or surgical intervention, no indication for surgical intervention, PSA $<$ 4.0 ng/mL, BMI $\leq$30 kg/m^2	IPSS, QoL score, Qmax, IIEF-5,	Low risk
Kim et al., 2017	Korea	62.1	Tamsulosin 0.4 mg/day plus tadalafil 5 mg/day	Unset	Tadalafil 5 mg/day	153	Unset	162	3 months	Men older than 50 years with BPH (total IPSS $\geq$13), ED for at least 3 months, Qmax of 4 to 15 mL/s, MVV $\geq$125 mL, PVR $>$ 300 mL, IIEF $\leq$25.	Toal IPSS, QoL, Qmax, PVR, IIEF-5, IPSS storage, IPSS voiding	Low risk
Sebastianelli et al., 2019	Italy	65.6	Tamsulosin 0.4 mg/day plus tadalafil 5 mg/day	Unset	Tadalafil 5 mg/day plus daily placebo	50	Unset	25	3 months	Men 40–80 years old with mild severe (IIEF-5 $<$ 22), moderate to severe LUTs (IPSS $>$ 7), Qmax $>$ 5	IPSS, Qmax, IIEF, IPSS storage, IPSS voiding, IPSS, QoL	Low risk
Nagasubramanian et al., 2020	India	60.1	Tamsulosin 0.4 mg/day plus tadalafil 5 mg/day	Tamsulosin 0.4 mg/day plus daily placebo	Unset	69	71	Unset	3 months	Men $\geq$45 years of age with moderate LUTs, IPSS 8–19, with peak urinary flow rate 5–15 mL/s	IPSS, IPSS QoL, IIEF, Peak flow, PVR	Low risk

Note. PDE5-Is = phosphodiesterase type 5 inhibitors; LUTS = lower urinary tract symptoms; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; tPSA = prostate specific-antigen; Qmax = maximum urine flow rate; QoL = quality of life; VAS = visual analogical scale; GAQ = global assessment quality; PVR = post-void residual; IIEF = International Index of Erectile Function; MVV = minimum voided volume; ED = erectile dysfunction.

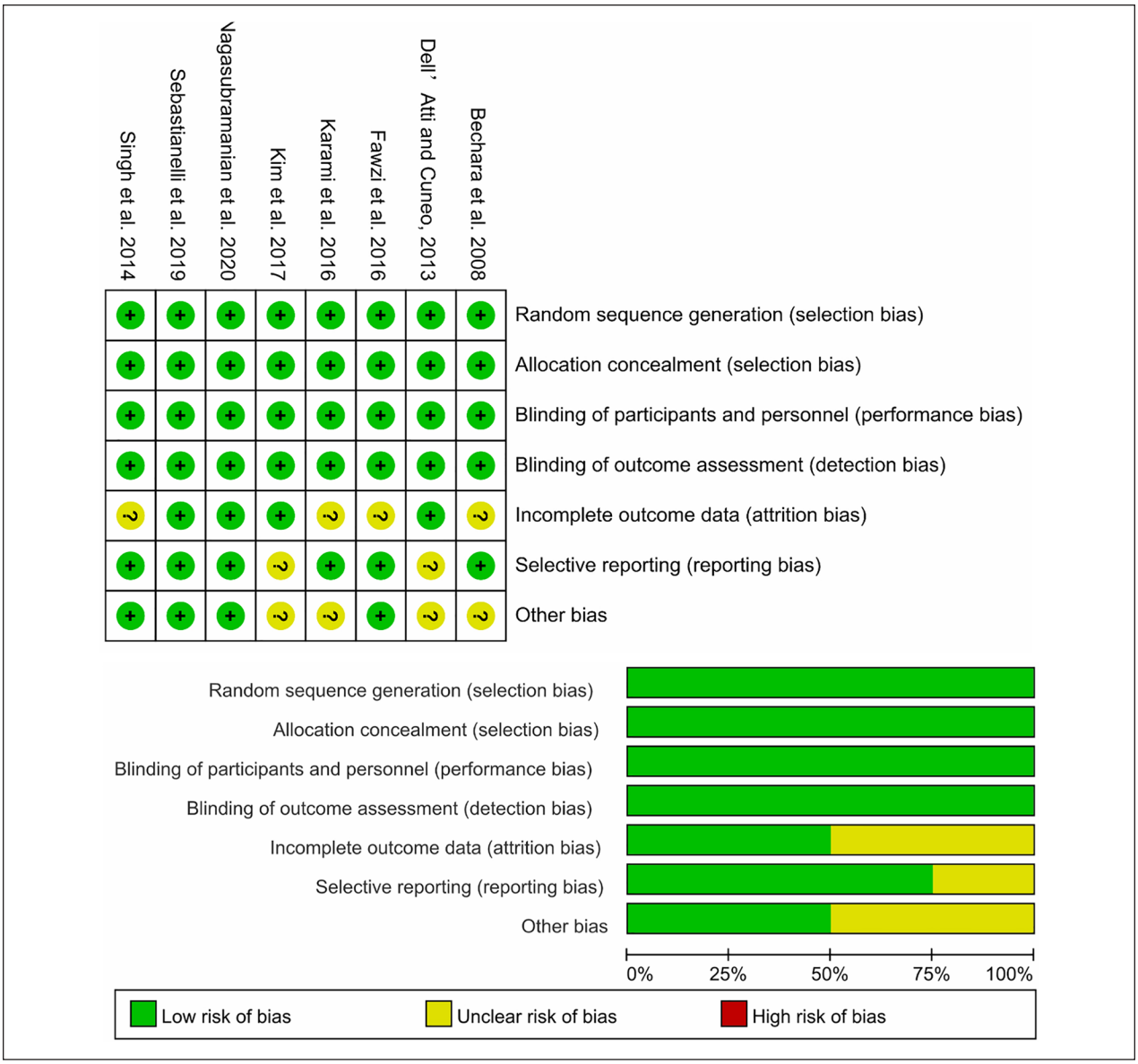

Figure 2. (a) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. (b) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

monotherapy (*MD* = 0.34, 95% CI [–0.65, 1.34], $p < .5$; Figure 5g).

Safety

Occurrence of AEs

Six RCTs comprising 601 patients (300 and 301 in the combination and tamsulosin groups, respectively) and five studies with 706 patients (360 and 346 in the combination and PDE5-Is groups, respectively) assessed the incidence of AEs. The combination therapy had a significantly higher incidence of AEs than tamsulosin (*OR* = 2.85, 95% CI [1.05, 7.76], $p = .04$; Figure 6a) and slightly higher than PDE5-Is (*OR* = 1.47, 95% CI [1.02, 2.13], $p = .04$) groups (Figure 7a).

Pain

Six RCTs comprising 601 patients (330 and 331, in the combination and tamsulosin groups, respectively) and five RCTs comprising 706 patients (360 and 346 in the combination and PDE5-Is groups, respectively) reported assessment of pain, including myalgia, back pain, headache, and bone pain. Results showed that the combination therapy generated significantly higher rates of pain

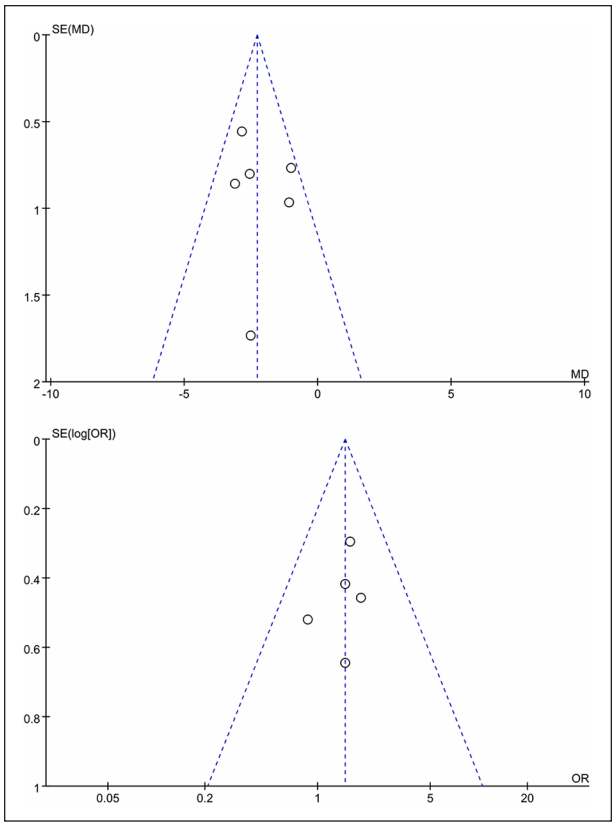

Figure 3. Funnel plot of the articles evaluating the efficacy of tamsulosin and PDE5-Is in combination with (a) tamsulosin alone and (b) PDE5-Is alone in the treatment of LUTS and ED. PDE5-Is = phosphodiesterase type 5 inhibitors; LUTS = lower urinary tract symptoms; ED = erectile dysfunction.

than tamsulosin monotherapy ($OR = 7.64$, 95% CI [3.33, 17.53], $p < .00001$; Figure 6b) but not PDE5-Is monotherapy ($OR = 1.45$, 95% CI [0.85, 2.48], $p = .17$; Figure 7b).

Discontinuation due to Pain and AEs

Six RCTs comprising 601 patients (300 and 301 in the combination and tamsulosin groups, respectively) and five RCTs with 631 patients (310 and 321 in the combination and PDE5-Is groups, respectively) reported therapy discontinuation due to pain and AEs. Results revealed no significant differences between the combination and tamsulosin groups ($OR = 1.47$, 95% CI [0.76, 2.84], $p = .25$; Figure 6c) as well as the combination and PDE5-Is groups ($OR = 1.69$, 95% CI [1.01, 2.84], $p = .05$; Figure 7c).

Discussion

BPH-related LUTS and ED increase with age; hence, physicians are expected to simultaneously manage them (Chitale et al., 2007; El-Sakka, 2006; Feldman et al., 1994). In addition, treatment approaches for ED and LUTS have been reported to influence each other, owing to an interaction between the two conditions. Currently, alpha-1 blockers are the most effective monotherapies for managing BPH-related LUTS. In fact, PDE5-Is represents the first line of action against ED (Committee, A. U. A. Practice Guidelines, 2003; Lue et al., 2004). Moreover, tamsulosin in combination with tadalafil is the only alpha-1 blocker approved for use. Consequently, it has received considerable attention from the medical community and is now combined with different PDE5-Is to develop more effective treatment options (Kloner, 2004).

In this meta-analysis, we effectively evaluated the efficacy and safety of a combination therapy comprising tamsulosin and PDE5-Is, relative to monotherapies for treatment of BPH-related LUTS and ED. Overall, our results indicated that patients who were administered with the combination therapy had significantly improved total IPSS and Qmax compared to those receiving tamsulosin or PDE5-Is monotherapies. The combination therapy also significantly ameliorated IIEF than tamsulosin monotherapy, but not relative to PDE5-Is monotherapy. Taken together, these results demonstrated that the combination therapy is more superior compared to tamsulosin in improving LUTS and ED but has only a slight effect compared to PDE5-Is monotherapy. We also found no evidence of advantage in sexual function.

Safety data suggested that administration of the combination therapy was well-tolerated. Therefore, we concluded that AE incidences in the combination group were significantly higher than those in both tamsulosin and PDE5-Is alone. Moreover, significantly higher incidences of pain were found in the combination group, relative to the tamsulosin group. However, the severity was mild or moderate and did not significantly affect the number of discontinuations due to AEs or pain, which was contrary to results from previous studies (Zhou et al., 2019). However, the included studies did not elaborate how the side effects arising from treatment were handled, which may lead to emotional fluctuation in patients during medication that could affect the final outcome. Therefore, we recommend preparation of approaches to deal with side effects as well as early elaboration of potential adverse reactions in patients during the designing of RCTs. Although tamsulosin-mediated IIEF amelioration has been described using parallel pathophysiological mechanisms shared by BPH-related LUTS and ED, the pharmacological mechanisms underlying the amelioration exhibited by the combination therapy remain unknown (McVary, 2006). Previous studies have hypothesized that both LUTS and ED might be synergistically affected by PDE5-Is and alpha-1 blockers due to the presence of two different working

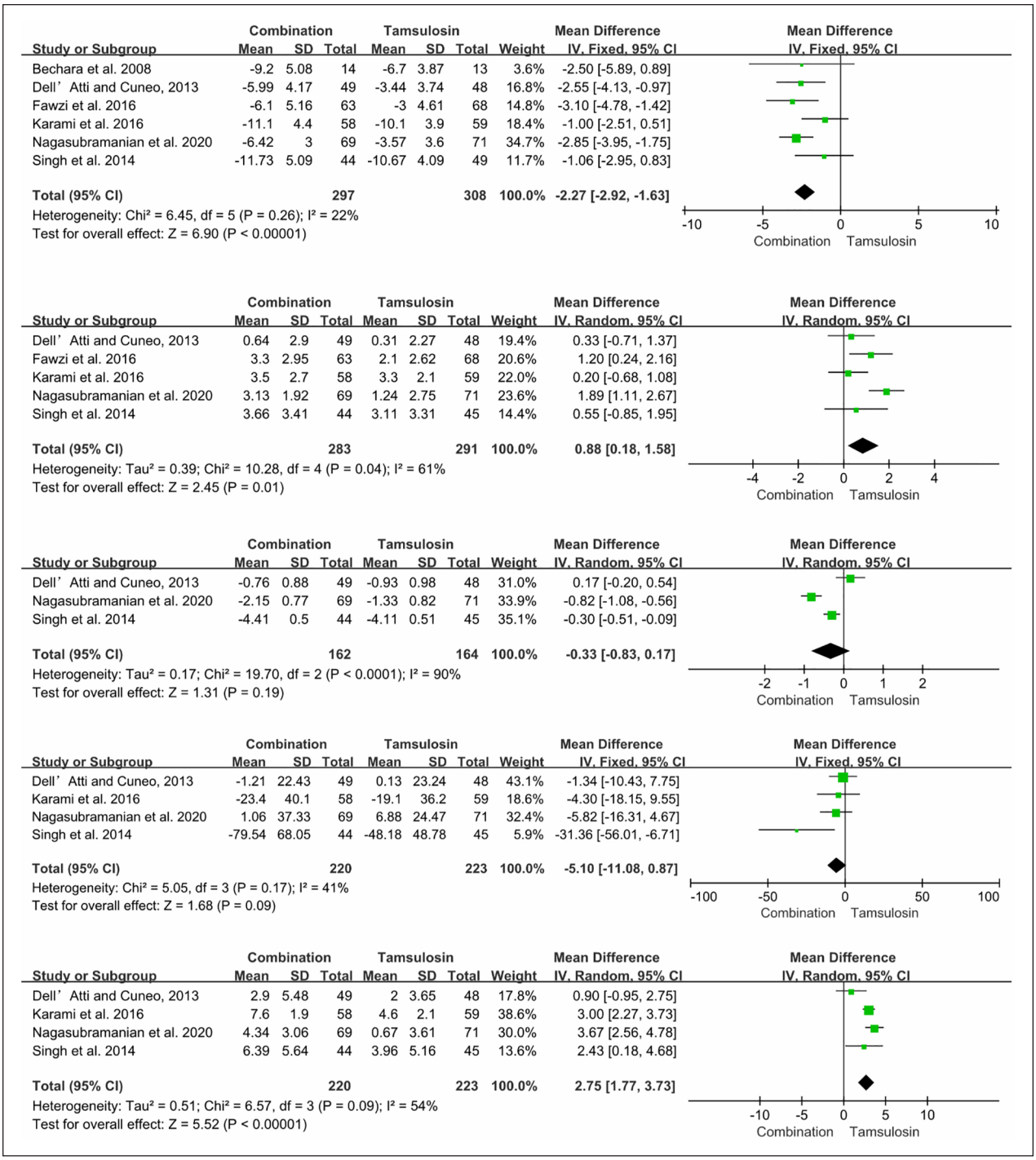

Figure 4. Forest plot comparing the change in (a) total IPSS, (b) Qmax, (c) QoL, (d) PVR, and (e) IIEF between the combination therapy and tamsulosin alone. IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; Qmax = maximum urine flow rate; QoL = quality of life; PVR = post-void residual.

mechanisms on common target organs of the urogenital system. Inhibiting alpha-1-adrenergic receptors as well as weakening the sympathetic tone in prostate/bladder neck and penile smooth muscle that alpha-1 blockers may potentially enhance PDE5-Is's NO-mediated flaccid impact (Bechara et al., 2008; Carson, 2006; Giuliano,

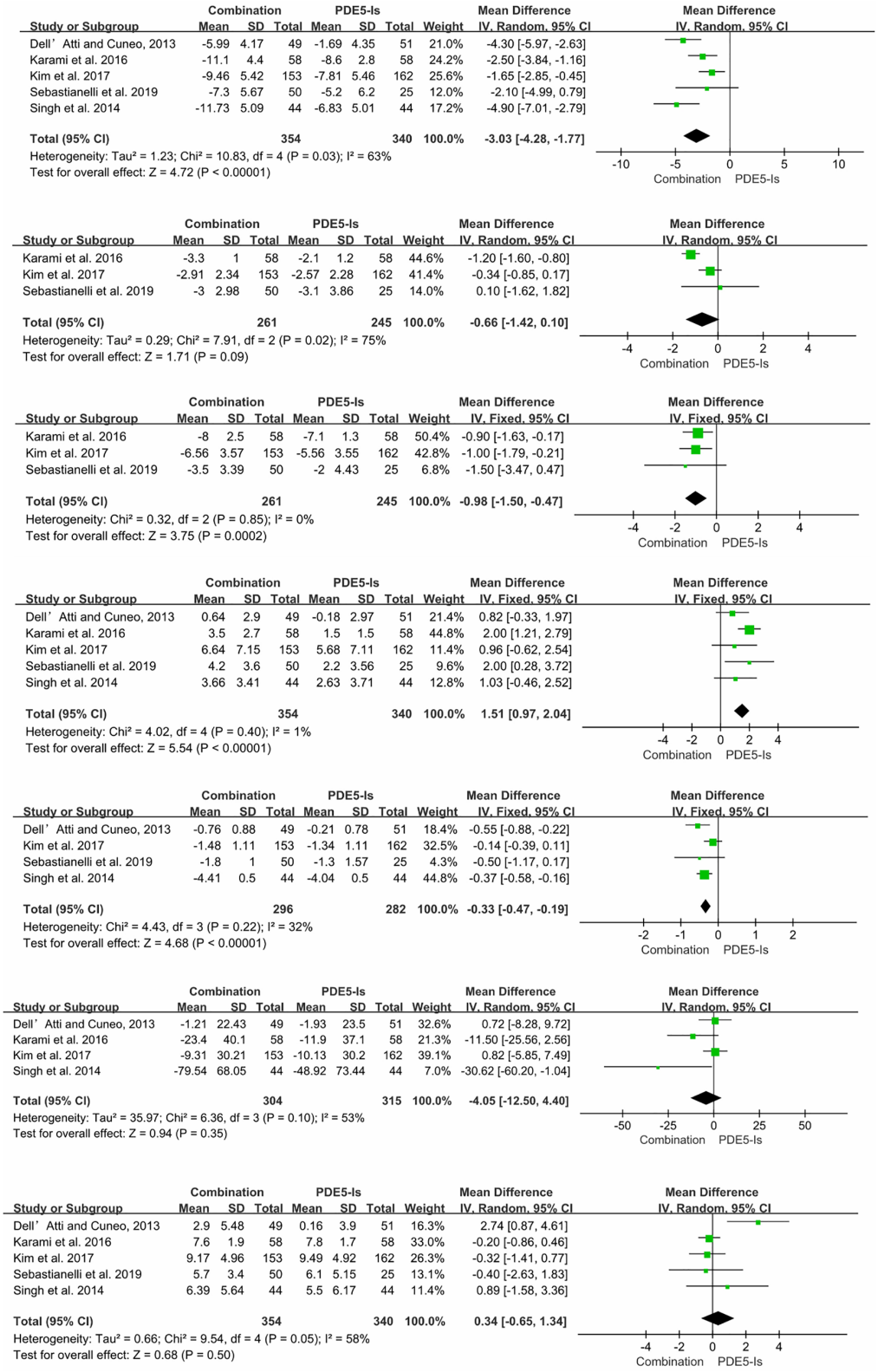

Figure 5. Forest plot comparing the change in (a) total IPSS, (b) IPSS storage, (c) IPSS voiding, (d) Qmax, (e) QoL, (f) PVR, and (g) IIEF between the combination therapy and PDE5-Is alone. IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; Qmax = maximum urine flow rate; QoL = quality of life; PVR = post-void residual.

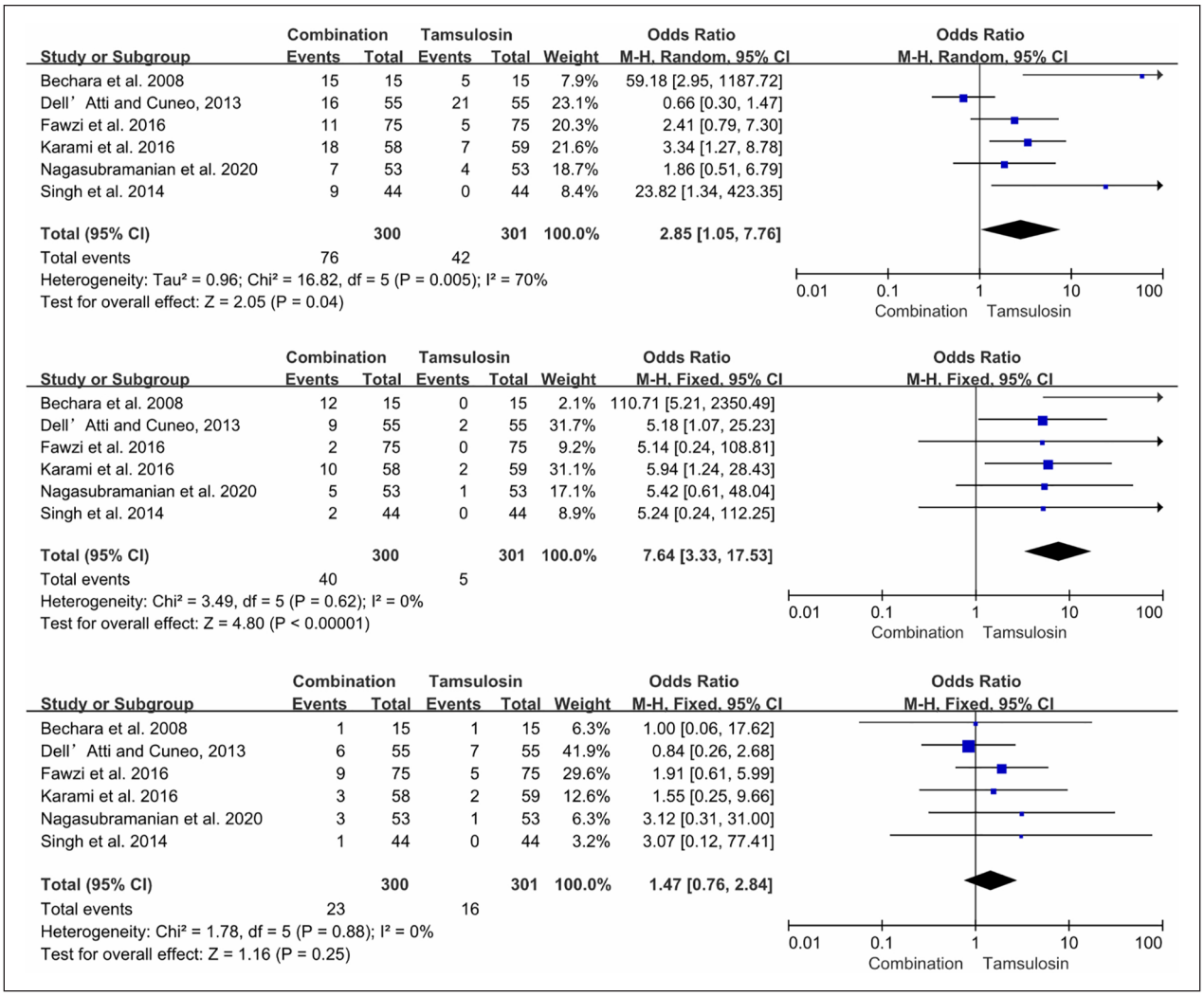

Figure 6. Forest plot comparing the change in numbers in (a) any AEs; (b) pain (including myalgia, back pain, headache, and bone pain); and (c) discontinuation due to pain and AEs between the combination therapy and tamsulosin alone. AEs = adverse events.

2008; Liguori et al., 2009; Mulhall et al., 2006; Oger et al., 2008). A previous study showed that PDE5-Is-mediated inhibition of the effects of alpha-1 blockers enhanced neurological contractions of human bladder neck and prostate (Angulo et al., 2012).

This meta-analysis had a few limitations. First, the long-term effect and safety of the reported combination therapy remains unclear. Second, it is possible that publication and selection bias as well as non-uniform therapy methods may influence the study outcomes. Third, the lack of variation in the choice of ED patients may lead to a large number of nonorganic ED patients, such as psychogenic ED, which may explain the poor efficacy in the treatment of sexual function. Advancements in medical science have led to development of more alpha-1 blockers and PDE5-Is. However, related clinical trials have either not been conducted or the results have not been published. This may generate inconsistent results. Additional high-quality RCTs, using larger sample sizes, are needed to comprehensively assess efficacy and safety of the aforementioned combination therapy for treating PBH-related LUTS and ED.

Conclusion

The combination therapy exhibited superior efficacy in treating BPH-related LUTS and ED, compared to tamsulosin and PDE5-Is monotherapies. Although the

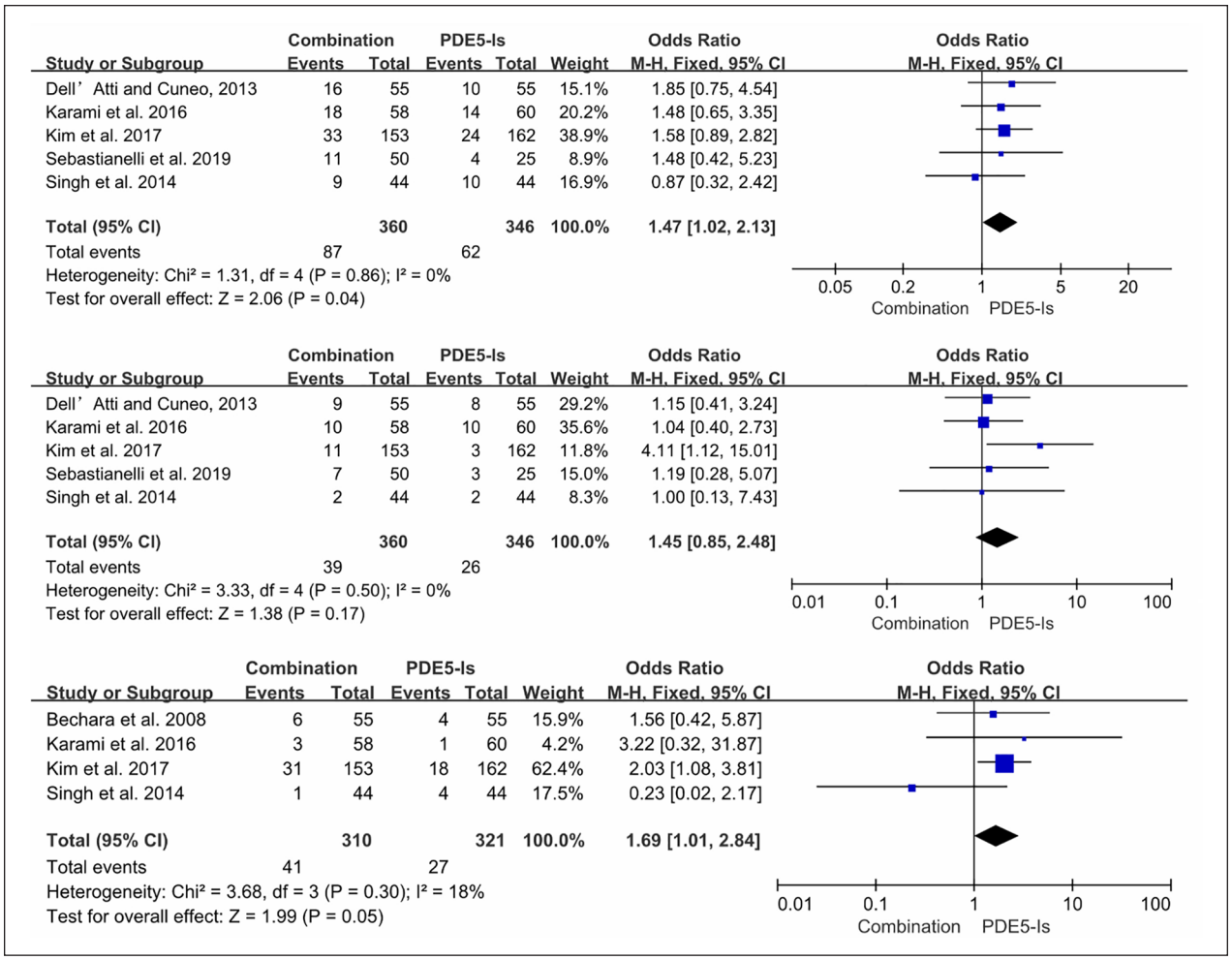

Figure 7. Forest plot comparing the change in numbers in (a) any AEs; (b) pain (including myalgia, back pain, headache, and bone pain); and (c) discontinuation due to pain and AEs between the combination therapy and PDE5-Is alone. AEs = adverse events; PDE5-Is = phosphodiesterase type 5 inhibitors.

combination therapy generated higher incidence of AEs than monotherapies, the effects were not severe and could be well tolerated.

Authors' Contribution

KS and FZS designed the research, analyzed the data, and wrote the draft manuscript. HBY, GW, and DXZ performed literature search, extracted and analyzed the data. JPW and TQW analyzed data and provided critical scientific input. JTW was responsible for resolving discrepancies regarding quality of the included studies, reviewing the manuscript, and providing critical scientific input. All authors made contribution to this article, read, and approved the final version.

Declaration of Conflicting Interests

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