Systematic review and meta-analysis of efficacy and safety of silodosin in treatment of benign prostatic hyperplasia patients with lower urinary tract symptoms

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Abstract

Background: Silodosin is a new high-selective α1A-adrenoceptors antagonist. A systematic review of literature and meta-analysis were performed to compare the clinical efficacy and safety outcomes of silodosin with placebo, tamsulosin, naftopidil and alfuzosin in treating benign prostatic hyperplasia (BPH) males with lower urinary tract symptoms (LUTS).

Materials and Methods: We systematically searched literature among EMBASE, PubMed, Cochrane Library, ScienceDirect and Web of Science databases until April 2019. 18 related randomized controlled trials were included according to eligibility criteria. Random-effects model were applied for data analysis.

Results: 5,985 patients were included in our study. Silodosin presented superiority to placebo in improving LUTS and better efficacy than tamsulosin and naftopidil in improving IPSS void subscore and post-void residual urine volume with statistically significance (all P values < 0.05). Greater QoL index improvement were found in silodosin than alfuzosin groups (MD = -0.44, 95%CI: [-0.83, -0.05], P = 0.03) while no differences in total IPSS score and Qmax changes between these two groups. Retrograde ejaculation was significantly frequent in silodosin than placebo, tamsulosin and naftopidil groups (all P values < 0.05). Besides, silodosin increased incidence of upper respiratory tract infection compared to tamsulosin groups (RR = 0.69, 95%CI: [0.50, 0.96], P = 0.03). A higher rate of nasal congestion (RR = 7.76, 95%CI: [1.80, 33.41], P = 0.006) were found in silodosin than placebo groups while no difference for nasopharyngitis ((RR = 1.16, 95%CI: [0.54, 2.47], P = 0.71). Prevalence of headache (RR = 0.54, 95%CI: [0.27, 1.06], P = 0.07) and postural hypotension (RR = 0.14, 95%CI: [0.03, 0.77], P = 0.02) were lower in silodosin than tamsulosin groups, although dizziness and vertigo was more frequent in silodosin than placebo (RR = 2.26, 95%CI: [1.21, 4.21], P = 0.009).

Conclusions: Our study demonstrated silodosin's possible superiority to placebo and naftopidil while noninferiority to tamsulosin and alfuzosin in LUTS improvement of BPH males. Better cardiovascular safety was in silodosin groups, although incidence of retrograde ejaculation and respiratory adverse events were higher.

Introductions

Benign prostatic hyperplasia (BPH) is a general chronic disease among elderly males. An epidemiological study conducted in mainland China indicates that approximately 36.6% of men older than 40 suffer from BPH, in which the pooled occurrence rate grows with age[1]. The clinical feature of BPH is LUTS with various symptoms like urinary urgency, frequency and urgency urinary incontinence and prevails among 62.8% males in parts of Asian[2]. Current medical therapies for LUTS/BPH contain conservative treatment for mild-to-moderate uncomplex symptoms; pharmacologic therapy for moderate-to-severe symptoms; and surgical interventions such as M-TURP for patients with enlarged prostate sizes from 30–80 ml or troublesome moderate-to-severe symptoms [3].

The pharmacologic therapy incorporating α1-adrenoceptor antagonists (α1-blockers), anticholinergic agents, 5α-reductase inhibitors, phosphodiesterase-5 inhibitors and vasopressin analogue are recommoned for LUTS/BPH patients, among which the α1-blockers (doxazosin, alfuzosin, tamsulosin, terazosin, indoramin, silodosin and naftopidil) are widely recommended as the first-line pharmacologic therapy for their rapid onset, exceptional efficacy, as well as their satisfactory tolerability and safety[3–5]. Previous studies have identified 4 pharmacologically different types of the α1-adrenergic receptor subfamily (α1A, α1B, α1D and a phenotype of the α1A-adrenoceptors, α1L), in which the α1A-and α1L-adrenoceptors predominate hyperplastic human prostate tissues overwhelmingly to medicate prostatic smooth muscle contraction while occur in relatively lower densities within vessels in patients 65 years or older[6, 7]. Blocking α1A-and α1L-adrenoceptors can result in smooth muscle relaxation to relieve symptoms and improve urinary flow. Differently, α1B-adrenoceptors and α1D-adrenoceptors distribute mainly in vascular smooth muscle for blood pressure regulation and detrusor muscle of the bladder for urine flow adjustment respectively[7].

Produced by Kissei Pharmaceutical Co., Ltd (Matsumoto, Japan) since 1990s, silodosin is a new high-selective α1A-and α1L-adrenoceptors antagonist approved in Japan in 2006, which was [8, 9]. More recently, both U.S. Food and Drug Administration and European Medicines Agency have approved silodosin for medical application [10]. Compared with non-selective α1-blockers, silodosin has higher affinity than prazosin in human prostate, 214 times higher than that in human aorta [11]. Additionally, apparently higher affinity for α1A-adrenoceptors was found in silodosin than α1B-adrenoceptors (593-fold) and α1D-adrenoceptors (57-fold)[12]. An in vivo study in 2019 has demonstrated that α1A-to-α1B binding ratio of silodosin was 9.8 times higher than that of tamsulosin despite they shared a similar affinity for α1A-adrenoceptors, clearly proving silodosin's highly selectivity for α1A-adrenoceptors[13]. These results illustrated that silodosin should allow the maximization of profitable effects on the symptoms related to LUTS/BPH to produce more favorable uroselectivity and minimal adverse effects on cardiovascular system. Several previous meta-analysis and sympathetic reviews have been conducted but the grouping method is not detailed due to a limited number of articles[14–17]. To date, more and more researches have evaluated the difference of efficacy and safety among silodosin and other medications whereas the results are controversial [18–35].Therefore, we decided to perform this meta-analysis through a

more detailed systematic review of those accessible RCTs to distinguish silodosin's superiority and non-inferiority to placebo and other medications in males with LUTS/BPH, which can provided more dependable guidance for the clinical application of silodosin.

Methods And Materials

Search strategy

A systematic search of the published literature was conducted among databases including EMBASE, PubMed, Cochrane Library, ScienceDirect, and Web of Science databases from their earliest dates until April 2019 to identify relevant researches based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[36]. We used and combined terms in our search strategy as follows: ('silodosin' OR 'KMD-3213') AND ('benign prostatic hypertrophy' OR 'benign prostatic hyperplasia' OR 'prostatic adenomas') AND 'lower urinary tract symptoms'. Specific generic and trade drug names like 'rapaflo' were included as well in our search. The references of the selected articles were also reviewed to avoid possible omission of potentially relevant publications.

Study Eligibility

The inclusion criteria were established before our search. Only RCTs in which patients with LUTS/BPH were grouped randomly to treat with silodosin or another mono-and combination medical therapy were included. We excluded in vitro studies, randomized crossover studies, surgery-controlled studies and observational studies without a control group. In cases that studies with analyses from the same data or duplicate study samples were classified, we preferentially evaluated the research with a larger sample size. All articles not related to the research topic, comments, editorials, conference proceedings, sympathetic review, meta-analysis articles, case reports or isolated abstracts are not included either. We didn't restrict the search strategy by publication year, sample-size or language.

Quality Assessment

The Cochrane System Evaluator Manual 5.1.0 were applied to assess the quality of included publications. The assessed aspects contain selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data); reporting bias (selective reporting) and other bias. We also used Begg's and Egger's test to estimate publication bias.

Endpoints Of Interest And Data Extraction

Two investigators extracted data independently from the qualified publications including basic information (authors, year of publication, geographical region), demographic information (e.g. patient age, prostate volume) and post-treatment endpoints. The primary endpoints of interest were the changes from the start of treatment for the total International Prostate Symptom Score (IPSS), the IPSS voiding subscore and the IPSS storage subscore, which all reflect changes of LUTS among males with BPH. Secondary endpoints of interest included the changes from the start of treatment for quality of life indexes (QoL), maximum urinary flow rate (Qmax), prostate size, post-void residual urine volume (PVR), adverse events (AEs) including retrograde ejaculation, postural hypotension, dizziness and vertigo, diarrhea, thirst, headache, nasopharyngitis and nasal congestion.

Statistical analysis

We collated the data extracted from included publications in Excel (Microsoft Corporation, Redmond, WA, USA) and then pooled for the summary estimates. Review Manager 5.3 (The Cochrane Collaboration) was used to perform meta-analysis. We applied random-effects model to calculate the risk ratio for dichotomous data, mean differences (MD) and standard deviations (SD) for continuous data, both with 95% confidence intervals (CI)[37]. The χ^2 statistic was applied to evaluate the heterogeneity among trials and I^2 statistic for the degree of inconsistency. In cases that data were not described by mean ± SD, the missing standard deviations for change scores were estimated using standard deviations from before and after the intervention[37].

Results

In total 1,456 articles have been identified during the primary search, among which 204 from PubMed, 398 from Web of Science, 407 from EMBASE, 354 from ScienceDirect and 93 from Cochrane Library. We excluded 1420 articles according to eligibility criteria. Among the remaining 36 potentially relevant publications, 18 were excluded for incomplete text and duplicate publications. In all, 18 articles with 28 RCTs

were included for data analysis (Supplementary Fig. 1). The quality assessment was shown in Supplementary Fig. 2. Most of the P value available accessed by Begg's and Egger's test were higher than 0.05, demonstrating the low risk of publication bias in our meta-analysis (Supplementary Table 1).

Study Characteristics

The basic characteristics were summarized in Supplementary Table 2. In total, 5985 patients were grouped randomly among the 18 articles, in which 2443 patients received silodosin 8 mg/day; 93 silodosin 4 mg/day; 1387, placebo; 672, tamsulosin 0.4 mg/day; 320, tamsulosin 0.2 mg/day; 201, naftopidil 75 mg/day; 79, naftopidil 50 mg/day; 117, alfuzosin 10 mg/day; 51, combination therapy. Various medical treatments were assessed, including 4 of the 28 RCTs compared silodosin with placebo, 10 RCTs with tamsulosin, 4 RCTs with naftopidil, 2 RCTs with alfuzosin, 2 RCTs with different dosage or administration of silodosin and 1 RCT with combination therapy (silodosin 8 mg/day and propiverine 20 mg/day). All studies applied silodosin 8 mg/day in males with LUTS/BPH. There are 7 trials in total had double blinded allocation for both outcome assessors and patients, 3 trials reported single blinded allocation for patients, 6 trials claimed open-label and 2 trials didn't mentioned the blinding method. The study follow-up time points included were 2, 4, 8 and 12 weeks. On the whole, 7 studies were conducted in Japan, 6 studies in India, one in Korea, one in Taiwan and the remaining 3 in Europe or/and USA. Mean patients age ranged from 50.0 to 71.5 years. Baseline total IPSS, void and storage scores ranged from 14.1 to 29.00, 7.47 to 13.0 and 6.3 to 8.9 points, respectively. Baseline prostate volumes, QoL, PVR and Qmax values ranged from 31.5 to 62.66 ml, 2.37 to 4.9 points, 28 to 92 ml and 7.297 to 15.9 ml/s, respectively.

Meta-analysis Of Efficacy

The total IPSS

The detailed outcomes of efficacy were shown in Table 1. 20 RCTs reported the total IPSS improvement and four kinds of medications were comprised in our meta-analysis. In total, silodosin demonstrated greater efficacy in the total IPSS improvement than placebo (MD = -2.69, 95%CI: [-3.10, -2.28], P < 0.05) (Supplementary Fig. 3a) while no statistically significant difference was found when compared with tamsulosin (MD = 0.41, 95%CI: [-0.50, 1.33], P = 0.38) (Supplementary Fig. 3b), naftopidil (MD = -0.89, 95%CI: [-2.08, 1.76], P = 0.15) (Supplementary Fig. 3c) and alfuzosin groups (MD = -0.16, 95%CI: [-2.39, 2.07], P = 0.89) (Supplementary Fig. 3d) as a whole. However, statistically significant difference existed between naftopidil and silodosin groups at 8 weeks from the start of the treatment (P < 0.05).

The IPSS Voiding Subscore

9 RCTs reported the IPSS voiding improvement. In total three kinds of medications were incorporated. The mean change from baseline to study end in IPSS voiding subscore is demonstrated the forest plots in Fig. 1. According to the total analysis, all the RCTs reported the same result that silodosin groups were associated with greater improvement in the IPSS voiding symptoms than placebo, tamsulosin and naftopidil groups, with MD = -1.79, 95%CI: [-2.06, -1.52], P < 0.05; MD = -0.47, 95%CI: [-0.90, -0.05], P = 0.03; MD = -1.17, 95%CI: [-2.18, -0.16], P = 0.02; respectively.

The IPSS Storage Subscore

9 RCTs reported the IPSS storage improvement. In total three kinds of medications were comprised. The mean change from baseline to study end in IPSS storage subscore is shown the forest plots in Fig. 2. According to the total analysis, silodosin was obviously more effective than placebo (MD = -0.87, 95%CI: [-1.05, -0.69], P < 0.05) and naftopidil (MD = -0.93, 95%CI: [-1.60, -0.26], P < 0.05) in the IPSS storage improvement whereas silodosin showed a non-inferior trend to tamsulosin but no statistically significant difference were found.

Qmax Changes

17 RCTs reported the Qmax changes. In total four kinds of medications were included in our meta. According to the total analysis, silodosin was only apparently more effective than placebo (Supplementary Fig. 4a) (MD = 1.24, 95%CI: [0.81, 1.67], P < 0.001) in Qmax improvement while no statistically significant differences occured between silodosin, tamsulosin (MD = -0.27, 95%CI: [-0.98, 0.44], P = 0.46) (Supplementary Fig. 4b), naftopidil groups (MD = -0.30, 95%CI: [-1.64, 1.03], P = 0.66) (Supplementary Fig. 4c) and alfuzosin (MD = 0.77, 95%CI: [-0.47, 2.02], P = 0.22) (Supplementary Fig. 4d).

QoL Changes

13 RCTs reported the QoL changes. In total four kinds of medications were included in our meta. Totally the QoL decreased more significantly after treatment in silodosin than in placebo (MD = -0.44, 95%CI: [-0.59, -0.28], P < 0.05) (Supplementary Fig. 5a) and alfzosin groups (MD = -0.44, 95%CI: [-0.83, -0.05], P = 0.03) (Supplementary Fig. 5d). On the contrary, there was no statistical significance found between silodosin and other two medications (tamsulosin and naftopidil) in QoL changes at all time points (P > 0.05) (Supplementary Fig. 5b and Supplementary Fig. 5c).

Prostate Size And PVR Changes

3 RCTs reported the prostate size and PVR changes. There were respectively one and two medications included in our meta. Silodosin was founded significantly effective in decreasing the prostate size (MD = -1.51, 95%CI: [-2.27, -0.76], P < 0.001) (Supplementary Fig. 6) and PVR (MD = -6.78, 95%CI: [-11.51, -2.06], P = 0.005) (Supplementary Fig. 7a) when compared with tamsulosin. Moreover, silodosin demonstrated apparent superiority over naftopidil in decreasing PVR (MD =-5.88, 95%CI: [-10.87, -0.89], P = 0.02) (Supplementary Fig. 7b).

Meta-analysis Of Safety

The detailed data of safety were shown in Table 2. The parameter we used to assess the safety of silodosin therapy is AEs. Overall adverse event rate was more frequent in silodosin than in tamsulosin (RR = 1.35, 95%CI: [1.19, 1.52], P < 0.00001) and alfuzosin groups (RR = 3.78, 95%CI: [1.00, 9.92], P = 0.05) with significant differences as shown in Supplementary Fig. 8, so as the incidence of drug-related adverse events when compared with two included medications (placebo, RR = 2.21, 95%CI: [1.20, 4.07], P = 0.01; tamsulosin, RR = 1.32, 95%CI: [1.16, 1.50], P < 0.00001) as shown in Supplementary Fig. 9. The most prevalent drug-related adverse events observed were retrograde ejaculation. The pooled results shown in Supplementary Fig. 10 demonstrated that retrograde ejaculation had a significantly higher incidence in silodosin than in placebo (RR = 24.39, 95%CI: [13.95, 42.64], P < 0.00001), tamsulosin (RR = 7.35, 95%CI: [4.55, 11.89], P < 0.00001) and naftopidil groups (RR = 6.54, 95%CI: [2.36, 18.15], P = 0.0003).

As for cardiovascular adverse events like dizziness and vertigo (Supplementary Fig. 11), statistically significant differences only exited between silodosin and placebo groups (RR = 2.26, 95%CI: [1.21, 4.21], P = 0.009). Conversely, incidence of headache was similar in placebo and silodosin groups, so as that of thirst and diarrhea when comparing silodosin with placebo (all P values > 0.05) (Supplementary Figs. 12, 13 and 14). However, the incidence of headache (RR = 0.54, 95%CI: [0.27, 1.06], P = 0.07) and postural hypotension (RR = 0.14, 95%CI: [0.03, 0.77], P = 0.02) were apparently lower in silodosin than in tamsulosin groups with statistical significance, indicating the better cardiovascular safety of silodosin (Supplementary Fig. 15).

In respiratory symptoms, silodosin could decrease more upper respiratory tract infection than tamsulosin (RR = 0.69, 95%CI: [0.50, 0.96], P = 0.03) (Supplementary Fig. 16) while increase nasal congestion significantly when compared to placebo (RR = 7.76, 95%CI: [1.80, 33.41], P = 0.006) (Supplementary Fig. 17). No statistical significance was attained between silodosin and placebo in nasopharyngitis (RR = 1.16, 95%CI: [0.54, 2.47], P = 0.71) (Supplementary Fig. 18).

Efficacy And Safety Results Of Administration-different And Combination Therapies

Due to limited number of articles and diverse treatment methods, the meta-analysis failed to be conducted among administration-different and combination therapies. For administration-different therapies, Choo et al.[33] compared application of silodosin at 8 mg once a day (QD) and 4 mg twice a day (BID) in Korean population in 2014. The results suggested the improvement and frequencies of AEs were similar in QD and BID group, which indicating silodosin in BID administration may not be superior to QD in improvement of treatment outcomes at a total dosage of 8 mg. In 2015, Seki et al.[34] evaluated the treatment outcomes between silodosin 4 mg BID and 4 mg QD in Japanese LUTS/BPH patients, in which statistically significant differences were not found in efficacy and safety endpoints despite ejaculation disorder was more frequent in former group. Results above indicated silodosin at 4 mg QD was not inferior to 4 mg BID. For combination therapies, Matsukawa et al.[35] assessed clinical efficacy and safety of monotherapy with silodosin only or combination therapy with silodosin and propiverine, an anticholinergic agent, after a long-term follow-up in Japanese males. The combination therapy group appeared statistically significant improvement in QoL index and PVR while similar improvement in changes of other efficacy endpoints after a one-year treatment, demonstrating better clinical performance of combination therapy with silodosin and propiverine for LUTS/BPH patients.

In conclusion, there was no statistical significance among different administration of silodosin according to included articles. In contrast, combination therapy with silodosin and propiverine showed superiority in efficacy of treatment. Of course, more highly qualified RCTs about administration-different and combination therapies are needed to be conducted for meta-analysis furthermore.

Discussion

BPH is the most pivotal and typical cause of LUTS in aged men and medicine treatment for BPH requires great effectiveness, affordable safety and reduced frequency of associated side effects, for which silodosin could be the potential ideal pharmacological therapy in recent years. As far as we know, this is the most comprehensive meta-analysis emphasizing on the clinical efficacy and safety outcomes of silodosin in treating aged BPH males accompanied with LUTS. Our study demonstrated that silodosin was effective and tolerable in treating LUTS related to BPH because it can apparently improve the total IPSS score, Qmax, IPSS storage and void subscore with statistically significant differences when compared with placebo. Besides, silodosin and tamsulosin shared the similar efficacy, except silodosin was superior in decrease of prostate size and improvement in IPSS void subscore and PVR. The better voiding symptoms improvement of silodosin may be for its higher α1A-adrenoceptors selectivity than tamsulosin as observed in some studies[13, 38].

The α1D-adrenoceptors predominate in bladder detrusor muscle, parasympathetic pathways and motor neurons in sacral ventral so blockage of them should result in storage symptoms improvement[39]. However, in our meta-analysis, silodosin was more effective in improvement of IPSS storage subscore, so as the IPSS void subscore and PVR in comparison of naftopidil, an α1D-adrenoceptors antagonist. The previous study has demonstrated that silodosin prohibits detrusor overactivity by suppressing C-fiber afferent activity in cerebral infarction rat models or increasing blood flow in the bladder of spontaneously hypertensive rat models[40, 41]. Therefore, blockade of α1A-adrenoceptors may improve the storage symptoms. Nevertheless, more studies should be conducted to compare the ability in storage symptoms improvement between α1A-and α1D-adrenoceptors antagonist. With regard to alfuzosin, a non-selective α1- adrenoceptors antagonist, these two drugs shared similar efficacy in improvement of total IPSS score and Qmax. However, silodosin was inferior in improving QoL index with a statistically significant difference which may be accounted for the clearly higher incidence of AEs in silodosin than alfuzosin (RR = 3.15, 95%CI: [1.00, 9.92], P = 0.05).

The incidence of drug-related adverse events was apparently higher in silodosin groups compared with tamsulosin and placebo groups. Among the AEs, it's remarkable that retrograde ejaculation had a significant higher incidence in silodosin groups when compared with placebo, tamsulosin, and naftopidil, which mainly led to discontinuation of therapy. Retrograde ejaculation could result from loosening of smooth muscle in the urethra, prostate, vas deferens and bladder neck along with reduced sperm movement through the posterior urethra [42]. The bladder neck, seminal vesicles and vas deferens of human have a high density of α1A-adrenoceptors, of which the highly selective blockade from silodosin can lead to more retrograde ejaculation than other therapies[7]. Additionally, Homma et al.[43] found ejaculation disorder may be relevant to better efficacy of silodosin in BPH, suggesting existence of ejaculation disorder can be a marker for classifying BPH patients with better improvement, which corresponds to the results of this meta-analysis.

Moreover, we have evaluated respiratory AEs in this meta-analysis. Obviously, silodosin led to more frequent nasal congestion but similar nasopharyngitis compared with placebo groups. Besides, upper respiratory tract infection was significantly less frequent in silodosin than in tamsulosin groups. The flu-like symptoms above have been reported in all sorts of α1-blockers, in which nasal congestion was a common one, for the blockade of α1A-adrenoceptors effecting the regulation of nasal mucosa blood flow rather than increasing the viral infection risk in upper respiratory tract [44]. However, the data of respiratory AEs were insufficient since only two articles were included in this part. More comparison in effects on respiratory tract among α1-blockers are required.

In our meta-analysis, the incidence of cardiovascular AEs like headache and postural hypotension was much lower in silodosin than in tamsulosin groups, although that of dizziness and vertigo was significantly higher than placebo, indicating the better cardiovascular safety of silodosin as supposed due to the higher selectivity of silodosin for α1A-adrenoceptors. Converse to the finding of favorable cardiovascular safety of the non-selective antagonist alfuzosin [45], we only observed a higher trend in incidence of dizziness and vertigo in silodosin compared with alfuzosin groups without a statistically significant difference. However, only two studies comparing silodosin and alfuzosin were included in this article, more high-quality clinical researches are needed to draw a reliable conclusion.

The heterogeneity of some variables greater than 70% in our meta-analysis is worthy of discussion. The reason for the high heterogeneity observed may be as follows. First, the recommended clinical dosages and administration of the medicine mentioned above are various in different countries and time. In the US, Europe and India, the recommend dosages of silodosin and tamsulosin were 8 mg/day and 0.4 mg/day respectively[18–20, 22–28]. However, silodosin at 4 mg twice a day was considered as effective as tamsulosin at 0.2 mg per day or naftopidil at 50 mg per day around the year of 2012 in Japan and other Asian areas[21, 29, 31], after which the recommended dosage change into silodosin at 8 mg, tamsulosin 0.4 mg and naftopidil at 75 mg every day respectively[30, 32]. The dosage variation may lead to the heterogeneity of our meta-

analysis, although tamsulosin 0.2 mg/day was a reasonable option for patients with low body mass index like Asians[46]while the recommended dosage of naftopidil was controversial [47, 48]. Therefore, the overall effect of dosage on our outcome analysis remains immeasurable. Moreover, the administration of silodosin differed from 4 mg twice a day to 8 mg once a day. Choo et al.[33] found no apparent statistical difference in efficacy and safety between silodosin 8 mg/day and 4 mg twice a day in Korean population. Therefore, we considered the administration of silodosin in all studies included as 8 mg per day regardless of the frequency. However, the performance bias may exist despite the total dosage seems to be equivalent. Second, although all the articles included patients with mild to moderate IPSS, the baseline scores were different. Patients with IPSS ≥ 7 or 8 in 12 trials[18, 22–25, 29–32, 34, 35] were included while IPSS ≥ 13 in 4 trials[19–21, 27]and no specific score requirement claimed in the remaining 2 trials[26, 28]. The different grade of baseline IPSS scores along with other different inclusion-exclusion criteria and sample size might influence the efficacy of medical therapy and result in selection bias to cause heterogeneity of some variables. Third, several follow-up time points like 4 weeks from the start of the treatment were not evaluated in some articles, in which clinical data at that time were in deficiency thus could increase the heterogeneity. Last but not the least, the articles we included were from different regions like USA, Europe, Japan, Taiwan, Korea and India. The diversity and disunities in races, gene, medical development level and environment could lead to the difference in the outcomes analyzed.

From this meta-analysis, we found that silodosin is an effective and safe medication for LUTS/BPH patients. Afterall, several limitations were existed in this meta-analysis. First, great heterogeneity still exists in some variables despite we applied a random effects model which may undervalue the statistical errors and defaults to the arithmetic mean in cases large heterogeneity exits[37]. Although we have divided groups according to the dosage of medicine, administration method and follow-up time, there were no more adequate data allowing to conduct a more detailed subgrouping to find the exact source of heterogeneity. Moreover, we were unable to take administration-different and combination therapies into meta-analysis due to insufficient number of articles. Second, the therapy period we evaluated was only short as 12 weeks. The comparison of long-term efficacy among α1-blockers requires more trials. Third, some included studies are of moderate quality. Therefore, after taking the heterogeneity of variables into consideration, our meta-analysis is necessary for assessment in silodosin's short-term clinical efficacy and safety at 8 mg per day compared with placebo and other α1-blockers. Even though, the findings of our meta-analysis need more high quality, especially meticulous long-term RCTs to demonstrate and confirm in the future.

Conclusions

In the current meta-analysis, we suggested silodosin may be superior to placebo and naftopidil while not inferior to tamsulosin and alfuzosin in improvement of LUTS relevant to BPH, and better cardiovascular safety was found in silodosin groups. However, the incidence of retrograde ejaculation was higher than in the placebo, tamsulosin, naftopidil and groups, as well as that of nasal congestion when compared with placebo groups. More stringent and long-term RCTs are required to confirm these conclusions.

Abbreviations

BPH
benign prostatic hyperplasia
RCTs
randomized controlled trials
LUTS
lower urinary tract symptoms
α1-blockers
α1-adrenoceptor antagonists
QoL
quality of life indexes
Qmax
maximum urinary flow rate
PVR
post-void residual urine volume
AEs
adverse events
QD
once a day
BID
twice a day

Declarations

Ethics approval and consent to participate

Not applicable (meta-analysis).

Consent for publication

Not applicable (meta-analysis).

Availability of data and materials

The data supporting the conclusions of this article are showed within the article and its supplementary files.

Competing interests

The authors declare that there is no conflict of interests regarding the publication of this article

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References

1. Wang W, Guo Y, Zhang D, et al. The incidence of benign prostatic hyperplasia in mainland China: evidence from epidemiological surveys. Sci Rep. 2015;5:13546.
2. Chapple C, Castro-Diaz D, Chuang YC, et al. Incidence of Lower Urinary Tract Symptoms in China, Taiwan, and South Korea: Results from a Cross-Sectional, Population-Based Study. Adv Ther. 2017;34(8):1953-65.
3. Oelke M, Bachmann A, Descazeaud A, et al. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Eur Urol. 2013;64(1):118-40.
4. Sarma AV, Wei JT. Clinical practice. Benign prostatic hyperplasia and lower urinary tract symptoms. The New England journal of medicine. 2012;367(3):248-57.
5. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol. 2011;185(5):1793-803.
6. Roehrborn CG, Schwinn DA. Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. The Journal of urology. 2004;171(3):1029-35.
7. Hennenberg M, Stief CG, Gratzke C. Prostatic α1-adrenoceptors: new concepts of function, regulation, and intracellular signaling. Neurourol Urodyn. 2014;33(7):1074-85.
8. Yoshida M, Homma Y, Kawabe K. Silodosin, a novel selective alpha 1A-adrenoceptor selective antagonist for the treatment of benign prostatic hyperplasia. Expert Opin Investig Drugs. 2007;16(12):1955-65.
9. Hwang EC, Gandhi S, Jung JH. New alpha blockers to treat male lower urinary tract symptoms. Current Opinion in Urology. 2018;28(3):273-6.
10. Jung JH, Kim J, MacDonald R, et al. Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. Cochrane Database of Systematic Reviews. 2017(11).
11. Murata S, Taniguchi T, Takahashi M, et al. Tissue selectivity of KMD-3213, an alpha(1)-adrenoreceptor antagonist, in human prostate and vasculature. J Urol. 2000;164(2):578-83.

12. Russo A, Hedlund P, Montorsi F. Silodosin From Bench to Bedside: Selectivity, Safety, and Sustained Efficacy. European Urology Supplements. 2011;10(6):445-50.
13. Quaresma BMCS, Pimenta AR, Santos da Silva AC, et al. Revisiting the Pharmacodynamic Uroselectivity of α 1-Adrenergic Receptor Antagonists. Journal of Pharmacology and Experimental Therapeutics. 2019;371(1):106-12.
14. Wu YJ, Dong Q, Liu LR, et al. A meta-analysis of efficacy and safety of the new alpha 1A -adrenoceptor-selective antagonist silodosin for treating lower urinary tract symptoms associated with BPH. Prostate Cancer and Prostatic Diseases. 2013;16(1):78-83.
15. Ding H, Du W, Hou Z-Z, et al. Silodosin is effective for treatment of LUTS in men with BPH: a systematic review. Asian Journal of Andrology. 2013;15(1):121-8.
16. Novara G, Tubaro A, Sanseverino R, et al. Systematic review and meta-analysis of randomized controlled trials evaluating silodosin in the treatment of non-neurogenic male lower urinary tract symptoms suggestive of benign prostatic enlargement. World Journal of Urology. 2013;31(4):997-1008.
17. Cui Y, Zong H, Zhang Y. The efficacy and safety of silodosin in treating BPH: A systematic review and meta-analysis. International Urology and Nephrology. 2012;44(6):1601-9.
18. Kawabe K, Yoshida M, Homma Y, et al. Silodosin, a new alpha(1A)-adrenoceptor-selective antagonist for treating benign prostatic hyperplasia: results of a phase III randomized, placebo-controlled, double-blind study in Japanese men. Bju International. 2006;98(5):1019-24.
19. Marks LS, Gittelman MC, Hill LA, et al. Rapid Efficacy of the Highly Selective alpha(1A)-Adrenoceptor Antagonist Silodosin in Men With Signs and Symptoms of Benign Prostatic Hyperplasia: Pooled Results of 2 Phase 3 Studies. Journal of Urology. 2009;181(6):2634-40.
20. Chapple CR, Montorsi F, Tammela TLJ, et al. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Urologiia (Moscow, Russia : 1999). 2012(5):38-42, 4-5.
21. Yu HJ, Lin ATL, Yang SSD, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). BJU International. 2011;108(11):1843-8.
22. Nabi N, Gupta S, Naikoo NN, et al. A Comparative Study of Silodosin And Tamsulosin in Treatment of Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperlasia Journal of Evolution of Medical and Dental Sciences-Jemds. 2016;5(77):5673-7.
23. Pande S, Hazra A, Kundu AK. Evaluation of silodosin in comparison to tamsulosin in benign prostatic hyperplasia: A randomized controlled trial. Indian Journal of Pharmacology. 2014;46(6):601-7.
24. Manjunatha R, Pundarikaksha HP, Madhusudhana HR, et al. A randomized, comparative, open-label study of efficacy and tolerability of alfuzosin, tamsulosin and silodosin in benign prostatic hyperplasia. Indian Journal of Pharmacology. 2016;48(2):134-40.
25. Yaraguppi AF, Ramesh H, Jadav R. A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF TAMSULOSIN AND SILODOSIN IN TREATMENT OF LOWER URINARY TRACT SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA. Journal of Evolution of Medical and Dental Sciences-Jemds. 2019;8(2):146-51.
26. Patil SB, Ranka K, Kundargi VS, et al. Comparison of tamsulosin and silodosin in the management of acute urinary retention secondary to benign prostatic hyperplasia in patients planned for trial without catheter. A prospective randomized study. Central European Journal of Urology. 2017;70(3):259-63.
27. Novara G, Chapple CR, Montorsi F. A pooled analysis of individual patient data from registrational trials of silodosin in the treatment of non-neurogenic male lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH). Bju International. 2014;114(3):427-33.
28. Manohar CMS, Nagabhushana M, Karthikeyan VS, et al. Safety and efficacy of tamsulosin, alfuzosin or silodosin as monotherapy for LUTS in BPH - a double-blind randomized trial. Central European Journal of Urology. 2017;70(2):148-53.
29. Yokoyama T, Hara R, Fukumoto K, et al. Effects of three types of alpha-1 adrenoceptor blocker on lower urinary tract symptoms and sexual function in males with benign prostatic hyperplasia. International Journal of Urology. 2011;18(3):225-30.
30. Matsukawa Y, Funahashi Y, Takai S, et al. Comparison of Silodosin and Naftopidil for Efficacy in the Treatment of Benign Prostatic Enlargement Complicated by Overactive Bladder: A Randomized, Prospective Study (SNIPER Study). Journal of Urology. 2017;197(2):452-7.
31. Shirakawa T, Haraguchi T, Shigemura K, et al. Silodosin versus naftopidil in Japanese patients with lower urinary tract symptoms associated with benign prostatic hyperplasia: A randomized multicenter study. International Journal of Urology. 2013;20(9):903-10.
32. Yamaguchi K, Aoki Y, Yoshikawa T, et al. Silodosin versus naftopidil for the treatment of benign prostatic hyperplasia: A multicenter randomized trial. International Journal of Urology. 2013;20(12):1234-8.
33. Choo M-S, Song M, Kim JH, et al. Safety and Efficacy of 8-mg Once-daily vs 4-mg Twice-daily Silodosin in Patients With Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (SILVER Study): A 12-Week, Double-blind, Randomized, Parallel, Multicenter

Study. Urology. 2014;83(4):875-81.
34. Seki N, Takahashi R, Yamaguchi A, et al. Non-inferiority of silodosin 4mg once daily to twice daily for storage symptoms score evaluated by the International Prostate Symptom Score in Japanese patients with benign prostatic hyperplasia: A multicenter, randomized, parallel-group study. International Journal of Urology. 2015;22(3):311-6.
35. Matsukawa Y, Takai S, Funahashi Y, et al. Long-term efficacy of a combination therapy with an anticholinergic agent and an alpha1-blocker for patients with benign prostatic enlargement complaining both voiding and overactive bladder symptoms: A randomized, prospective, comparative trial using a urodynamic study. Neurourol Urodyn. 2017;36(3):748-54.
36. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.
37. Perera M, Roberts MJ, Doi SA, et al. Prostatic urethral lift improves urinary symptoms and flow while preserving sexual function for men with benign prostatic hyperplasia: a systematic review and meta-analysis. Eur Urol. 2015;67(4):704-13.
38. Tatemichi S, Kobayashi K, Maezawa A, et al. Alpha1-adrenoceptor subtype selectivity and organ specificity of silodosin (KMD-3213). Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan. 2006;126 Spec no.:209-16.
39. Széll EA, Yamamoto T, de Groat WC, et al. Smooth muscle and parasympathetic nerve terminals in the rat urinary bladder have different subtypes of alpha(1) adrenoceptors. British journal of pharmacology. 2000;130(7):1685-91.
40. Yokoyama O, Ito H, Aoki Y, et al. Selective α1A-blocker improves bladder storage function in rats via suppression of C-fiber afferent activity. World J Urol. 2010;28(5):609-14.
41. Inoue S, Saito M, Tsounapi P, et al. Effect of silodosin on detrusor overactivity in the male spontaneously hypertensive rat. BJU Int. 2012;110(2 Pt 2):E118-24.
42. Nagai A, Hara R, Yokoyama T, et al. Ejaculatory dysfunction caused by the new alpha1-blocker silodosin: A preliminary study to analyze human ejaculation using color Doppler ultrasonography. Int J Urol. 2008;15(10):915-8.
43. Homma Y, Kawabe K, Takeda M, et al. Ejaculation disorder is associated with increased efficacy of silodosin for benign prostatic hyperplasia. Urology. 2010;76(6):1446-50.
44. Oelke M, Gericke A, Michel MC. Cardiovascular and ocular safety of α1-adrenoceptor antagonists in the treatment of male lower urinary tract symptoms. Expert Opin Drug Saf. 2014;13(9):1187-97.
45. Akinaga J, García-Sáinz JA, A SP. Updates in the function and regulation of α -adrenoceptors. British journal of pharmacology. 2019;176(14):2343-57.
46. Shim SR, Kim JH, Choi H, et al. General effect of low-dose tamsulosin (0.2 mg) as a first-line treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia: a systematic review and meta-analysis. Curr Med Res Opin. 2015;31(2):353-65.
47. Funahashi Y, Hattori R, Matsukawa Y, et al. Clinical efficacy of a loading dose of naftopidil for patients with benign prostate hyperplasia. World J Urol. 2011;29(2):225-31.
48. Oh-oka H. Usefulness of naftopidil for dysuria in benign prostatic hyperplasia and its optimal dose--comparison between 75 and 50 mg. Urol Int. 2009;82(2):136-42.

Tables

Table 1. Results of meta-analysis on the changes from baseline for efficacy endpoints of silodosin and other medications at different time points

Efficacy endpoints	Medication	MD 95%CI	*P*	MD 95%CI	*P*	MD 95%CI	*P*	MD 95%CI	*P*	MD 95%CI	*P*
		Overall		2 weeks		4 weeks		8 weeks		12 weeks	
The IPSS total	Silodosin VS placebo	-2.69 [-3.10, -2.28]	<0.00001	-	-	-	-	-	-	-2.69 [-3.10, -2.28]	<0.00001
	Silodosin VS tamsulosin	0.41[-0.50, 1.33]	0.38	-0.29 [-1.62, 1.05]	0.68	0.25[-1.85, 2.35]	0.82	-0.65 [-1.51, 0.21]	0.14	1.04 [-0.64, 2.72]	0.22
	Silodosin VS naftopidil	-0.89 [-2.08, 1.76]	0.15	-0.75 [-3.57, 2.07]	0.6	-	-	-3.22 [-5.76, -0.76]	0.01	-0.28 [-2.33, 1.76]	0.79
	Silodosin VS alfzosin	-0.16 [-2.39, 2.07]	0.89	-	-	-0.94 [-2.58, 0.70]	0.26	-	-	0.89 [-2.39, 6.09]	0.74
The IPSS voiding subscores	Silodosin VS placebo	-1.79 [-2.06, -1.52]	<0.00001	-	-	-	-	-	-	-1.79 [-2.06, -1.52]	<0.00001
	Silodosin VS tamsulosin	-0.47 [-0.90, -0.05]	0.03	-0.30 [-1.44, 0.84]	0.61					-0.50 [-0.96, -0.04]	0.03
	Silodosin VS naftopidil	-1.17 [-2.18, -0.16]	0.02	-	-	-1.15 [-3.39, 1.10]	0.32	-2.10 [-3.72, -0.48]	0.01	-0.80 [-1.80, 0.20]	0.12
The IPSS storage subscores	Silodosin VS placebo	-0.87 [-1.05, -0.69]	<0.00001	-	-	-	-	-	-	-0.87 [-1.05, -0.69]	<0.00001
	Silodosin VS tamsulosin	-0.21 [-0.50, 0.08]	0.15	-0.20 [-0.95, 0.55]	0.6	-	-	-	-	-0.21 [-0.52, 0.10]	0.18
	Silodosin VS naftopidil	-0.93 [-1.60, -0.26]	0.006	-	-	-0.93 [-2.30, 0.43]	0.18	-1.70 [-2.89, -0.51]	0.005	-0.60 [-1.24, 0.04]	0.07
Qmax	Silodosin VS placebo	1.24 [0.81, 1.67]	<0.00001	-	-	-	-	-	-	1.24 [0.81, 1.67]	<0.00001
	Silodosin VS tamsulosin	-0.27 [-0.98, 0.44]	0.46	0.30 [-0.18, 0.78]	0.22	-0.08 [-1.97, 1.81]	0.93			-0.42 [-1.41, 0.57]	0.4
	Silodosin VS naftopidil	-0.30 [-1.64, 1.03]	0.66	-	-	-0.23 [-1.30, 0.83]	0.67	0.10 [-2.76, 2.96]	0.95	-0.48 [-4.32, 3.36]	0.81
	Silodosin VS alfzosin	0.77 [-0.47, 2.02]	0.22	-	-	1.33 [0.39, 2.27]	0.006	-	-	0.23 [-2.39, 2.84]	0.87
Prostate size	Silodosin VS tamsulosin	-1.51 [-2.27, -0.76]	<0.00001	-	-	-1.89 [-9.22, 5.44]	0.61	-	-	-1.51 [-2.27, -0.75]	<0.00001
PVR	Silodosin VS tamsulosin	-6.78 [-11.51, -2.06]	0.005	2.20 [-2.99, 7.39]	0.41	-7.97 [-14.22, -1.72]	0.01	-	-	-8.24 [-16.22, -2.06]	0.04
	Silodosin VS naftopidil	-5.88 [-10.87, -0.89]	0.02	-	-	-3.44 [-6.14, -0.73]	0.01	-7.50 [-50.20, 35.20]	0.73	-8.83 [-15.11, -2.56]	0.006
QoL	Silodosin VS placebo	-0.44 [-0.59, -0.28]	<0.00001	-	-	-	-	-	-	-0.44 [-0.59, -0.28]	<0.00001
	Silodosin VS tamsulosin	-0.20 [-0.42, 0.02]	0.07	-0.10 [-0.40, 0.20]	0.51	-0.16 [-0.71, 0.38]	0.55	-0.18 [-0.55, 0.19]	0.34	-0.25 [-0.68, 0.19]	0.26

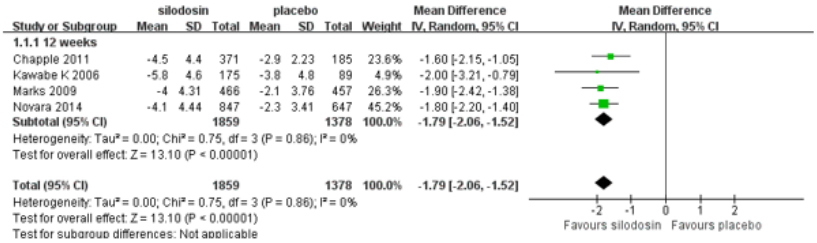
Silodosin VS naftopidil	-0.18 [-0.38, 0.02]	0.07	-	-	-0.18 [-0.56, 0.02]	0.35	-0.42 [-1.01, 0.16]	0.16	-0.17 [-0.73, 0.38]	0.54
Silodosin VS alfzosin	-0.44 [-0.83, -0.05]	0.03	-	-	-0.77 [-0.99, -0.55]	<0.00001	-	-	-0.21 [-0.83, -0.05]	0.44

Table 2. Results of meta-analysis on the safety endpoints of silodosin and other medications at different time points

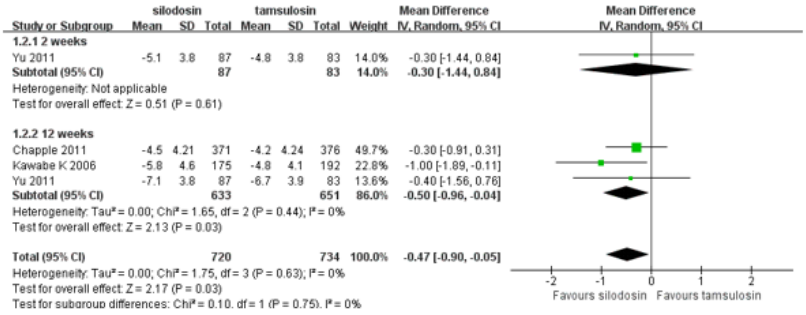
Safety Endpoints	Medication	OR 95%CI	*P*	RR 95%CI	*P*	RR 95%CI	*P*	RR 95%CI	*P*	RR 95%CI	*P*
		Overall		2 weeks		4 weeks		8 weeks		12 weeks	
Retrograde ejaculation	Silodosin VS placebo	24.39 [13.95, 42.64]	<0.00001	-	-	-	-	-	-	24.39 [13.95, 42.64]	<0.00001
	Silodosin VS tamsulosin	7.35 [4.55, 11.89]	<0.00001	-	-	10.75 [2.07, 55.81]	0.005	-	-	7.10 [4.30, 11.73]	<0.00001
	Silodosin VS naftopidil	6.54 [2.36, 18.15]	0.0003	-	-	10.22 [1.36, 76.61]	0.02	-	-	5.61 [1.72, 18.31]	0.004
Dizziness & vertigo	Silodosin VS placebo	2.26 [1.21, 4.21]	0.01	-	-	-	-	-	-	2.26 [1.21, 4.21]	0.01
	Silodosin VS tamsulosin	1.18 [0.78, 1.79]	0.43	-	-	1.56 [0.68, 3.57]	0.3	-	-	1.08 [0.67, 1.74]	0.76
	Silodosin VS alfzosin	1.93 [0.32, 11.54]	0.47	-	-	25.28 [1.53, 418.86]	0.02	-	-	0.83 [0.46, 1.51]	0.55
Headache	Silodosin VS placebo	1.23 [0.51, 2.95]	0.64	-	-	-	-	-	-	1.23 [0.51, 2.95]	0.64
	Silodosin VS tamsulosin	0.54 [0.27, 1.06]	0.07	-	-	-	-	-	-	0.54 [0.27, 1.06]	0.07
Upper respiratory tract infection	Silodosin VS tamsulosin	0.69 [0.50, 0.96]	0.03	-	-	-	-	-	-	0.69 [0.50, 0.96]	0.03
Postural hypotension	Silodosin VS placebo	1.43 [0.74, 2.76]	0.29	-	-	-	-	-	-	1.43 [0.74, 2.76]	0.29
	Silodosin VS tamsulosin	0.14 [0.03, 0.77]	0.02	-	-	-	-	-	-	0.14 [0.03, 0.77]	0.02
Any adverse events	Silodosin VS placebo	1.13 [0.37, 3.45]	0.83	-	-	-	-	-	-	1.13 [0.37, 3.45]	0.83
	Silodosin VS tamsulosin	1.35[1.19, 1.52]	<0.00001	-	-	1.37 [0.74, 2.54]	0.32	-	-	1.32 [1.12, 1.57]	0.001
	Silodosin VS naftopidil	1.02 [0.07, 15.85]	0.99	-	-	-	-	-	-	1.02 [0.07, 15.85]	0.99
	Silodosin VS alfzosin	3.15 [1.00, 9.92]	0.05	-	-	6.24 [1.92, 20.25]	0.002	-	-	1.96 [1.01, 3.77]	0.05
Drug-related adverse events	Silodosin VS placebo	2.21 [1.20, 4.07]	0.01	-	-	-	-	-	-	2.21 [1.20, 4.07]	0.01
	Silodosin VS tamsulosin	1.32 [1.16, 1.50]	<0.00001	-	-	-	-	-	-	1.32 [1.16, 1.50]	<0.00001
Thirst	Silodosin VS placebo	2.04 [0.84, 5.00]	0.12	-	-	-	-	-	-	2.04 [0.84, 5.00]	0.12
Diarrhea	Silodosin VS placebo	1.74 [0.89, 3.38]	0.1	-	-	-	-	-	-	1.74 [0.89, 3.38]	0.1

Nasopharyngitis	Silodosin VS placebo	1.16 [0.54, 2.47]	0.71	-	-	-	-	-	-	1.16 [0.54, 2.47]	0.71
Nasal congestion	Silodosin VS placebo	7.76 [1.80, 33.41]	0.006	-	-	-	-	-	-	7.76 [1.80, 33.41]	0.006

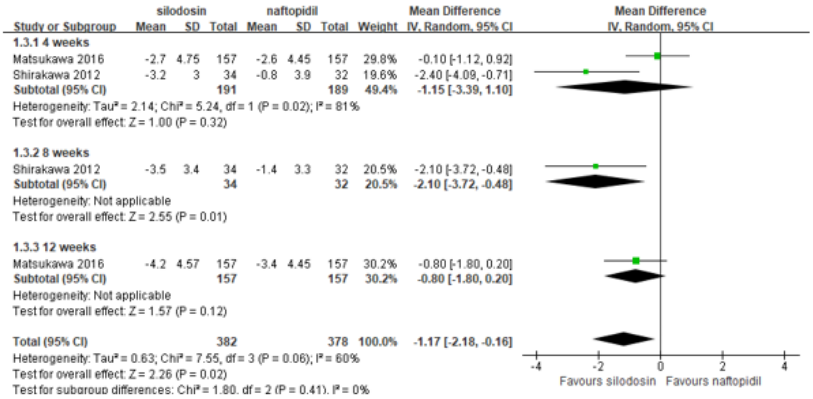
Figures



(a) Silodosin versus placebo



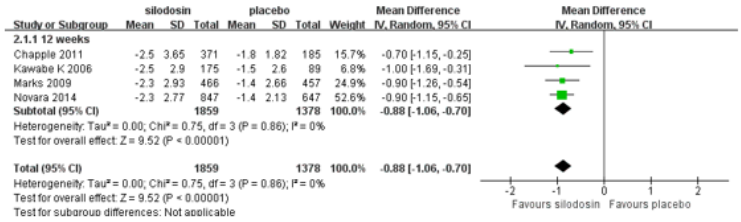
(b) Silodosin versus tamsulosin



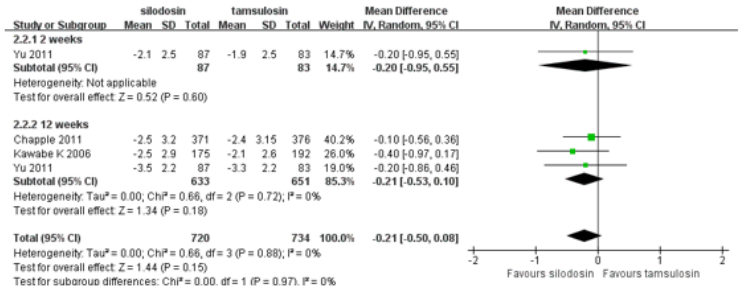
(c) Silodosin versus naftopidil

Figure 1

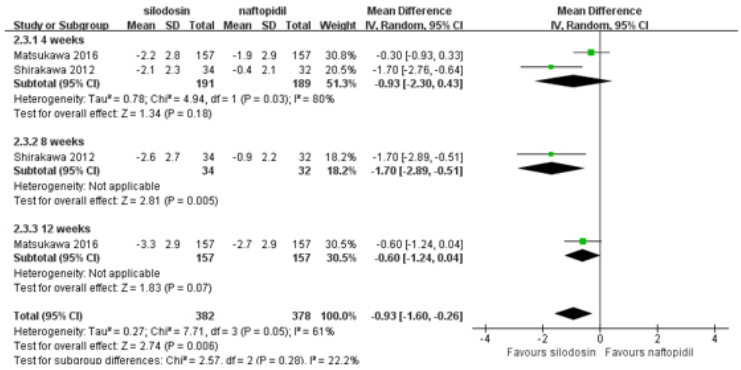
Results of the meta-analysis on the change from baseline for the IPSS voiding subscore at different time points (silodosin versus placebo, tamsulosin and naftopidil, respectively). Statistically significant differences were found in silodosin compared with tamsulosin and naftopidil at 12 and 8 weeks from the start of the treatment respectively ($P < 0.05$).



(a) Silodosin versus placebo



(b) Silodosin versus tamsulosin



(c) Silodosin versus naftopidil

Figure 2

Results of the meta-analysis on the change from baseline for the IPSS storage subscore at different time points (silodosin versus placebo, tamsulosin and naftopidil, respectively). Statistically significant differences were found in silodosin compared with naftopidil at 8 weeks from the start of the treatment ($P < 0.05$).

Supplementary Files

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