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Efficacy of Mirabegron Compared with Tolterodine, Placebo, and Different Doses of Mirabegron on OAB Patient Evaluated in 4 Weeks Period: A Meta-Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. Authors CNP, GWKD and PMWT did the concepts of this study. Authors CNP, KI, KAW, GWKD and PMWT did the design and definition of intellectual content of this study. Literature search and data acquisition done by authors CNP, KI and KAW. Authors CNP, KI, KAW, GWKD and PMWT did the data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review and guarantor. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Mirabegron is one of the therapeutic options in overactive bladder where its efficacy and safety are better than antimuscarinics in several existing studies. Tolerability, treatment duration, and cost are often the deciding points for patient adherence and compliance in taking treatments. Many patients and doctors expect fast and visible results with relatively short treatments duration. This meta-analysis study describes and compares the efficacy of mirabegron compared with antimuscarinic, placebo or different doses of mirabegron over 4 weeks' treatment range.

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Methods: A literature search was performed using the Cochrane Library, Pubmed, and 5 other journal database. The literature reviewed included randomized and nonrandomized prospective and clinical trial studies. Mean difference (MD) was used to assess micturition frequency, incontinence episode, mean volume voided, nocturia episodes, urgency episodes, urgency incontinence episodes, and level of urgency of patients recorded within 4 weeks treatment duration. We used the Cochrane Collaboration's Review Manager 5.4.1 software for statistical analysis

Results: Six publications that met eligibility criteria was included in this study. Meta-analysis of extractable data showed that Mirabegron was found significantly more efficacious than placebo for majority of efficacy endpoints recorded within 4 weeks' treatment duration. In contrast, the comparison of mirabegron with tolterodine 4 mg showed no significant difference in outcome across all seven assessment criteria. On the other hand, mirabegron was also found to be more efficacious when administered in higher doses compared to lower doses at the majority efficacy endpoint

Conclusion: Withtin 4-week treatment duration, Mirabegron can provide significant results compared to placebo. However, the results are still not much different from tolterodine. Higher doses of mirabegron also provide a better result when compared with lower doses. The lowest dose with statistically significant results compared to placebo was obtained from mirabegron 25 mg.

Keywords: Mirabegron; tolterodine; efficacy; overactive bladder; meta-analysis.

1. INTRODUCTION

International Continence Society defines overactive bladder (OAB) syndrome as urinary urgency with or without urinary incontinence, usually followed by increased daytime frequency and nocturia, without sign of urinary tract infection or other apparent pathology. OAB Patients will have a lower quality of life due to impaired physical, social, emotional, and sexual function [1,2].

Several studies reported prevalence of OAB were 11.8% - 35.6% in western countries and 15.8% - 23.9% in Asian countries with female predominant [3,4]. They also reported prevalence of OAB increased with age in both men and women. The epidemiological study held in three Asian countries (Taiwan, China and South Korea) also reported that the prevalence of OAB was higher in women, population aged ≥ 40 years [4]. This result was similar to the EPIC and NOBLE study held in Europe and United States [3,4].

The current guidelines for OAB treatment still suggest pharmacotherapy following the conservative approach. Antimuscarinic and β3 – adrenergic receptor agonists are still recommended as monotherapy or in combination for patients who did not respond to monotherapy [5]. Antimuscarinics usage has been known to induce discomforting side effects such as dry mouth, constipation, headache, and blurred vision. Among the antimuscarinics agents, tolterodine is a new drug commonly used to treat OAB and has lower incidence of adverse effects than other antimuscarinics [6,7]. Prior studies about antimuscarinics persistence and adherence showed only 28-58% of patients obedient to therapy after three months and decreased to 20-40% at six months. There were 65-86% of OAB patients discontinued antimuscarinics due to insufficient symptoms control and/or excessive adverse effect over 12 months [7,8,9].

β3 – adrenergic receptor agonist is a relatively newer type of drug found to treat OAB. β3 – adrenergic receptor agonist relaxes detrusor muscle in the bladder without impaired bladder contraction during the voiding phase. Therefore, it can improve bladder capability to store urine in OAB patients without voiding symptoms. Mirabegron is a potent and selective β3 – adrenergic receptor agonist approved for OAB treatment by the FDA in 2012 and followed by its European counterparts in 2013 [10]. Mirabegron is still a relatively new drug with multiple dosages have been reported among clinical trials. Therapeutic doses have been reported between 25 to 100 mg in several clinical trials. Meanwhile, earliest onset of Mirabegron's efficacy was reported at 4 weeks in phase III trials [7,10].

Prolonged treatment of OAB was followed by increased side effects, low adherence of patients on therapy, and increased rate of treatment discontinuation. The high dropout rate of patients

on long-term treatment may also affect the results of previous research analyzes. Therefore, we carried out this study to evaluate the lowest optimal dose in the shortest possible time where the dropout rate is still small. This study aimed to perform a meta-analysis and systematic review to compare and describe the efficacy of different dosages of Mirabegron for treatment of OAB, compared with tolterodine and placebo within four weeks of treatments.

2. METHODS

We conducted a systematic literature search in PubMed, Cochrane. Google Scholar, USC library, Sage journal, Biomed Central, and Europe PMC in May 2021. We identify relevant studies We used specific keywords, adjusted to each search engine specification using the keyword (Mirabegron) AND (efficacy) AND (overactive bladder or OAB). The meta-analysis was conducted and reported based on Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [11].

2.1 Study Selection and Data Extraction

The eligibility criteria of the studies included in this review were: (i) Randomized Clinical Trial studies evaluating efficacy and safety of Mirabegron compared to placebo and/or tolterodine followed within four weeks of treatment. (ii) No restriction regarding country, patient age, race, gender, publication language and date. (iii) Provide sufficient data regarding outcomes that could be analyzed. The exclusion criteria of this review were: (i) Study in non-human subjects. (ii) Articles that were not available in full-text format.

Two reviewers independently screened the articles' abstract and title to exclude irrelevant studies. Then a full-text screen was performed for potential articles. Both reviewers discussed their findings and any discordant results consulted to the third reviewer. The reviewers extracted basic information about the study such as the study's title, study design, sample size, therapies given in the study, when and where the studies are conducted, baseline demographics and clinical characteristics of the study participants.

2.2 Outcome and Quality Assessment

We evaluate the mean difference to assess the efficacy of Mirabegron in various doses compared to tolterodine and placebo. The efficacy parameters we assessed are mean difference in the number of micturition per 24 hours, incontinence per 24 hours, volume voided per micturition, nocturia episodes per 24hours, urgency episodes per 24 hours, urgency incontinence episodes per 24 hours, and level of urgency. We used Cochrane's risk-of-bias tools for RCT (RoB 2) for assessing the risk of bias. The result was classified as "Low Risk", "High Risk", or "uncertain" by two reviewers of the study. Any discordant assessments consulted for the third opinion.

Data analysis used in this study is Review Manager Software (RevMan v.5.4.1, Cochrane Collaboration, Oxford, UK). Random effect analysis was performed regardless of the statistical heterogeneity, based on the assumption that most studies have quantitative heterogeneity. The heterogeneity was assessed using Cochrane's Q test and I2 statistics, in which I2 values above 50% and p-value below 0.10 indicate significant heterogeneity. Mean differences with a 95% Confidence Interval (CI) were calculated to estimate the efficacy parameters. We will present the result of this study in forest plots.

3. RESULTS

3.1 Characteristic and Quality of the Studies

A total of 684 journals and articles were obtained after a search using all accessible databases. From the screening results of titles and abstracts, 32 studies were found that were related to the study criteria. After further review, 26 of them did not have the required data according to the inclusion criteria, so a total of 6 studies were included in this study. The detailed study filtering shown in Fig. 1. Data from the 6 studies can be seen in Table 1. The six studies used were RCTs and double-blinded. Quality assessment of each journal is described in Fig. 2.

3.2 Efficacy

For each parameter assessed, three meta-analyses were performed comparing mirabegron with placebo, mirabegron with tolterodine 4 mg, and mirabegron with different doses of mirabegron.

3.2.1 Mean number of micturition/24 hours

In the Mirabegron vs placebo analysis, we identified five trials with mirabegron and placebo

data. In total, 3569 patients from the three intervention groups (Mirabegron 25 mg, 50 mg, and 100 mg) contributed to the mean number of micturition/24 hours data. High there was high heterogeneity found between trials, so we use a random-effects model for analysis. The random effect model mean difference (MD) was -0.40 (95% CI -0.47, -0.33; *P*<.00001), indicating mirabegron had a statistically significant effect compared with placebo in the mean number of micturition/24 h when evaluated in 4 weeks. Two trials were used in the comparison of Mirabegron with Tolterodine 4 mg analysis. A total of 2531 patients contributed to this analysis. Random effect model MD acquired was -0.06 (95%CI -0.17, 0.05; *P*= .27), meaning that there was no statistically significant difference was found in total mirabegron comparison, but when we viewed more specifically, Mirabegron 100mg statistically have a significant reduction of the mean number of micturition compared with tolterodine 4 mg when evaluated in 4 weeks, with random effect model MD of -0.13 (95%CI -0.24, -0.03; *P*= .01). (Fig. 3. A and B).

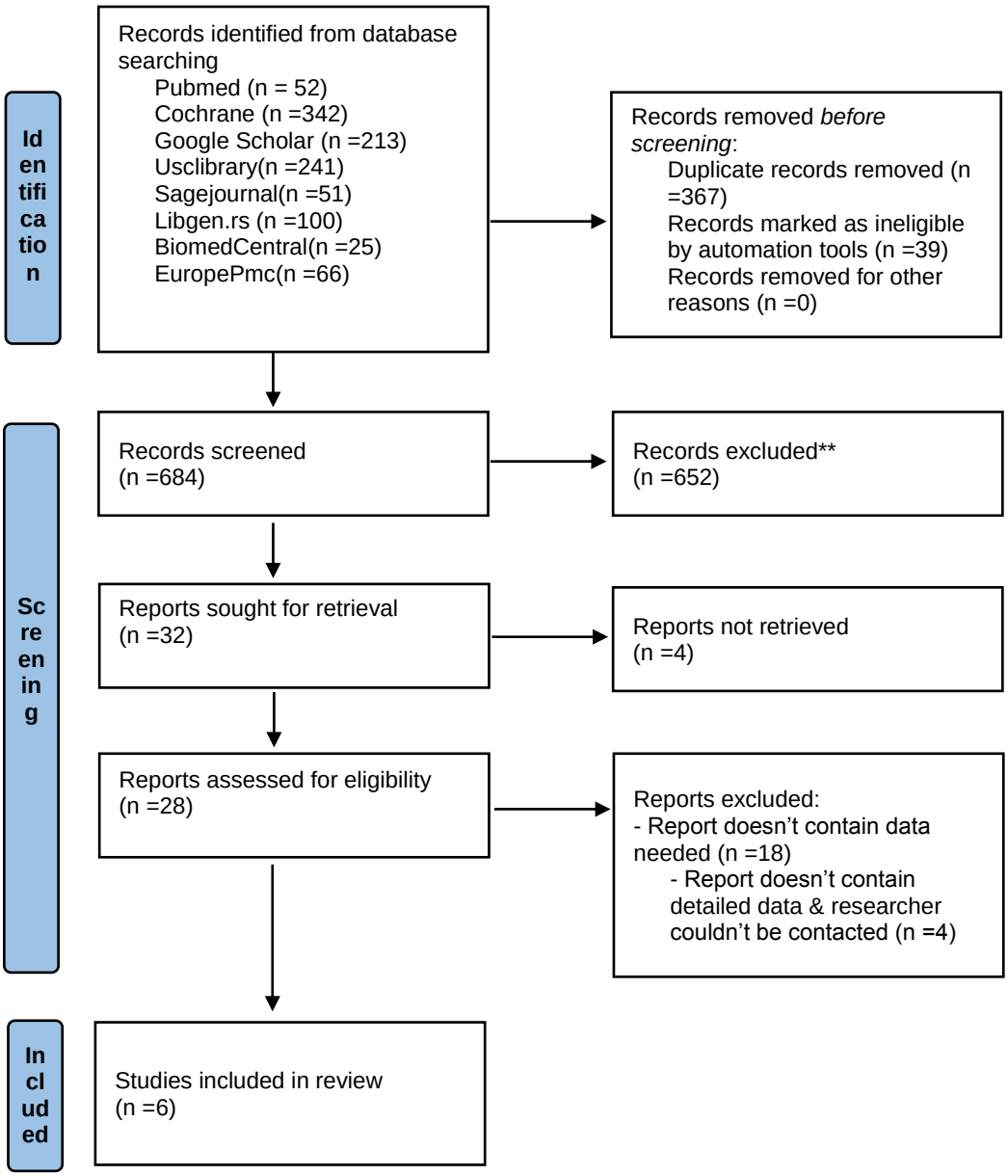

Fig. 1. Flow diagram of search strategy and study selection based on Preffered Reporting Items for systematic Reviews and Meta-analyses Statement (PRISMA)

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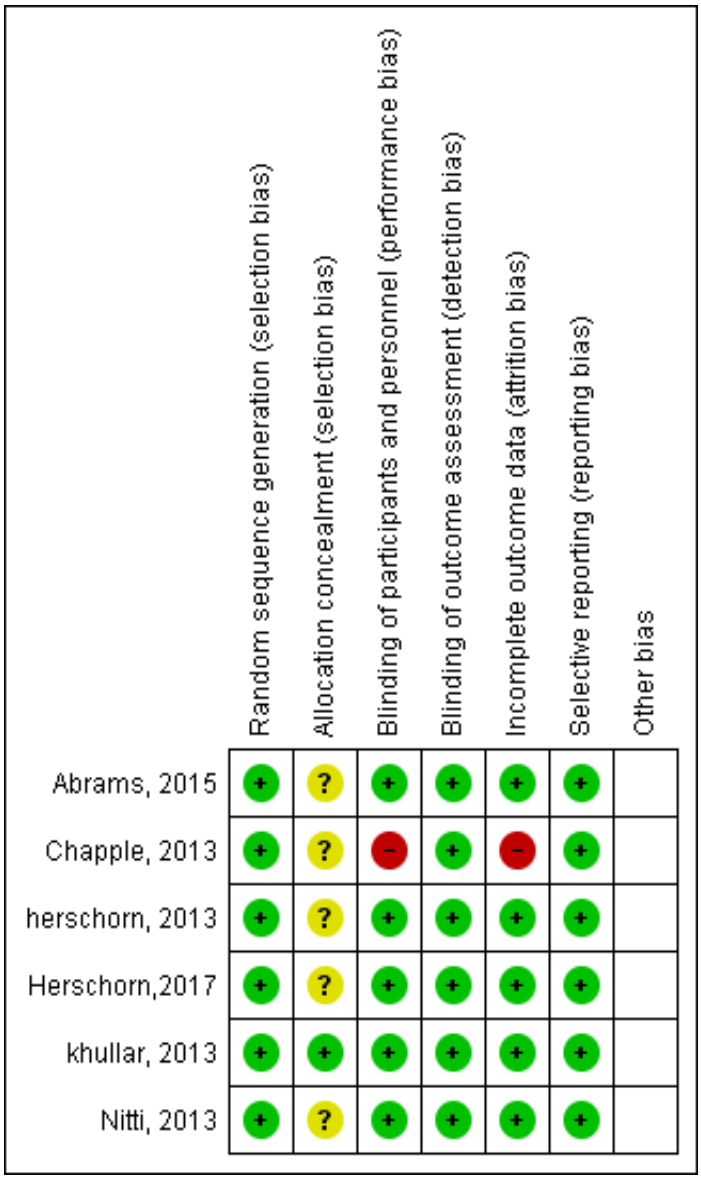

Fig. 2. Quality assessment of each journal

When compared with different doses of mirabegron, the analysis showed a statically significant reduction found in mirabegron with higher doses compared to the lower doses, random effect model MD was -0.11 (95%CI -0.17, -0.05; *P*= .0005). (Fig. 3. C).

3.2.2 Incontinence episode/24 hours

A total of 2523 patients contributed to the mirabegron vs placebo analysis. The random effect model MD was -0.34 (95% CI -0.39, -0.28; *P*<.00001), where it can be concluded that mirabegron had a statistically significant reduction compared with placebo in incontinence episode/24 hours. (Fig. 4. A).

In mirabegron with tolterodine 4 mg analysis, the random effect model MD acquired was -0.12 (95%CI -0.26, 0.02; *P*= .15). No statiscally significant difference was found between mirabegron and tolterodine in reducing incontinence episodes/24 hours evaluated in 4 weeks. (Fig. 4. B).

However, in different doses of mirabegron analysis, there was a statically significant reduction found in mirabegron with higher doses compared with lower doses with random effect model MD of -0.02 (95%CI -0.18, -0.05; *P*= .0010). (Fig. 4. C).

Table 1. Summary of the included Studies

Study	Journal Type, Blinding	National Clinical Trial Number (NCT)	Country	Interventions and control	Total Sample	Inclusion Criteria
Abrams et al. (2015)	RCT, Double blind	NCT01340027	141 sites in 20 European countries	Mirabegron 25mg Mirabegron 50mg Solifenacin 2.5mg Solifenacin 5 mg Solifenacin 10mg Placebo 6 Combination theraphy	1306	male and female patients >18 yr with symptoms of OAB (urgency, urinary frequency, and/or urgency incontinence) 3 mo. patients with eight or more micturitions per 24 h and one urgency episode or more per 24 h (with or without incontinence), based on a 3-d electronic patient micturition diary
Chapple et al. (2013)	RCT, Double blind	NCT00688688	306 sites in Europe, the United States, Canada, South Africa, Australia, and New Zealand	Mirabegron 50mg Mirabegron 100mg Tolterodine ER 4mg	2444	Patients 18 yr of age : 1. Symptoms of OAB (urinary frequency and urgency with/without incontinence) for 3 mo 2. Frequency of micturition on average eight or more times per 24 h during the 3-d micturition diary period 3. Three or more episodes of urgency (grade 3 or 4) with/without incontinence during the 3-d micturition diary period
Herschorn et al. (2013)	RCT, Double blind	NCT00912964	151 sites in Europe (56 sites) and North America (95 sites)	Mirabegron 25mg Mirabegron 50mg Placebo	1305	Patients 18 yr of age : 1. patients with an average 8 micturitions per 24 hours 2. three urgency episodes (grade 3 or 4 on the 5-point Patient Perception of Intensity of Urgency Scale) with or without incontinence
Herschorn et al. (2017)	RCT, Double blind	NCT01972841	NR	Mirabegron 25mg Mirabegron 50mg Solifenacin 5mg Placebo Combination theraphy (Mirabegron 25 + Solifenacin, ETC)	3527	Patients aged ≥18 years who had had symptoms of wet OAB (urgency, urinary frequency and UI) for ≥3 months 1. average ≥8 micturitions/24 h, ≥1 urgency episode/24 h (grade 3 or 4 on the Patient Perception of Intensity of Urgency Scale [PPIUS]/24 h), and ≥3 UI episodes over the 7-day micturition diary
Kullar et al. (2013)	RCT, Double blind	NCT00689104	189 sites in 27 countries in Europe and Australia	Mirabegron 50mg Mirabegron 100mg Tolterodine ER 4mg Placebo	1978	men and women 18 yr of age with symptoms of OAB for 3 mo : 1. average micturition frequency of eight or more times per 24-h period 2. at least three episodes of urgency, with or without incontinence, during a 3-d micturition diary period
Nitti et al. (2013)	RCT, Double blind	NCT00662909	132 sites in the United States and Canada	Mirabegron 50mg Mirabegron 100mg Placebo	1328	Male and female patients 18 years old or older ,had OAB symptoms for 3 or more months : an average of 8 or more micturitions per 24 hours and 3 or more urgency episodes (grade 3—severe urgency or grade 4—urge incontinence) with or without incontinence during a 3-day period, and must have continued.

RCT = Randomized Controlled Trial, NR= Not Reported, OAB = Overactive Bladder

3.2.3 Mean volume voided/micturition

Mirabegron was found statistically more significant than placebo in increasing mean volume voided/micturition, with random effect MD of 9.13 (95% CI 7.04, 11.22; *P*<.00001). This analysis includes a total of 3554 patients from five different studies. (Fig. 5. A).

Nevertheless, Mirabegron showed no significant result compared with tolterodine in increasing the mean volume voided/micturition, random effect MD 1.50 (95% CI -3.80, 6.80; *P*= .58). On top of that, in this fourweeks' analysis, tolterodine showed a more significant result when compared only with Mirabegron 50 mg with random effect MD of -2.60 (95%CI -5.15, -0.05; *P*= .05). (Fig. 5. B).

Same as the previous analysis, higher doses of mirabegron showed a better and statistically significant result when compared to lower doses in increasing the volume voided/micturition within fourweeks treatment period, random effect MD 5.55 (95%CI 3.55, 7.55; *P*<.00001). (Fig. 5. C).

3.2.4 Nocturia episode/24 hours

In mirabegron vs placebo analysis, the random effect model MD was -0.09 (95% CI -0.13, -0.06; *P*<.00001), where mirabegron have a statistically significant result compared with placebo. However, from a more detailed analysis, it can be found that mirabegron 25 mg has not been able to provide better results when compared to placebo in reducing the incidence of nocturia recorded within four weeks. (Fig. 6. A).

Both Mirabegron vs tolterodine and different doses of mirabegron comparison showed no significant reduction in reducing nocturia incidence, with random effect MD 0.00 (95%CI -0.03, 0.03; *P*=1.00) and -0.04 (95%CI -0.08, 0.01; *P*= .13) respectively. (Fig. 6. B and C).

3.2.5 Urgency episode/24 hours

Analysis of mirabegron and placebo in reducing urgency episodes also showed some significant results with the random effect model MD -0.43 (95% CI -0.56, -0.30; *P*<.00001) where mirabegron is superior. Like the previous analysis, mirabegron 25 mg failed to show a significant result compared with placebo in 4 weeks' treatment period analysis. (Fig. 7. A).

There was no difference between mirabegron and tolterodine treatment results, where the random effect model was 0.07 (95%CI -0.05, 0.19; *P*= .28). Conversely, just like the previous analysis, higher doses of mirabegron showed superior results with random effect model MD -0.19 (95%CI -0.35, -0.04; *P*= .02). (Fig. 7. B and C).

3.2.6 Urgency incontinence Episode/24 hours

Total 2467 mirabegron intervention's data were used for urgency incontinence episodes in mirabegron vs placebo analysis. The random effect model MD was -0.31 (95% CI -0.37, -0.24; *P*<.00001), showing some statistically significant results from mirabegron. (Fig. 8. A).

Mirabegron and tolterodine comparison analysis showed no difference between the two interventions with a random effect model of -0.01 (95%CI -0.07, 0.06; *P*= .88). Meanwhile, higher doses mirabegron was superior compared to lower doses mirabegron with random effect model -0.12 (95%CI -0.18, -0.05; *P*= .0005). (Fig. 8. B and C).

3.2.7 Level of Urgency (grade 3 or 4)/24 hours

In mirabegron vs placebo analysis, the random effect model MD was -0.05 (95% CI -0.08, -0.02; *P*= .001), where mirabegron is superior. Data were collected from 4 studies with a total of 2748 patient data from the intervention group. (Fig. 9. A).

The random effect model MD acquired for mirabegron and tolterodine data was -0.00 (95%CI -0.02, 0.01; *P*= .73), meaning that no statistically significant difference was found in total mirabegron comparison. (Fig. 9. B).

Comparison between the different doses of mirabegron analysis also showed that higher doses of mirabegron statistically yield a better result in decreasing level of urgency with random effect model -0.03 (95%CI -0.06, 0.00; *P*= .04). (Fig. 9. C).

3.3 Funnel Plot of the Studies

The six studies included were plotted into funnel plot and it shown an asymmetrical distribution particularly on the study with higher standard error (study with small sample size) as shown on the bottom right corner. (Fig. 10).

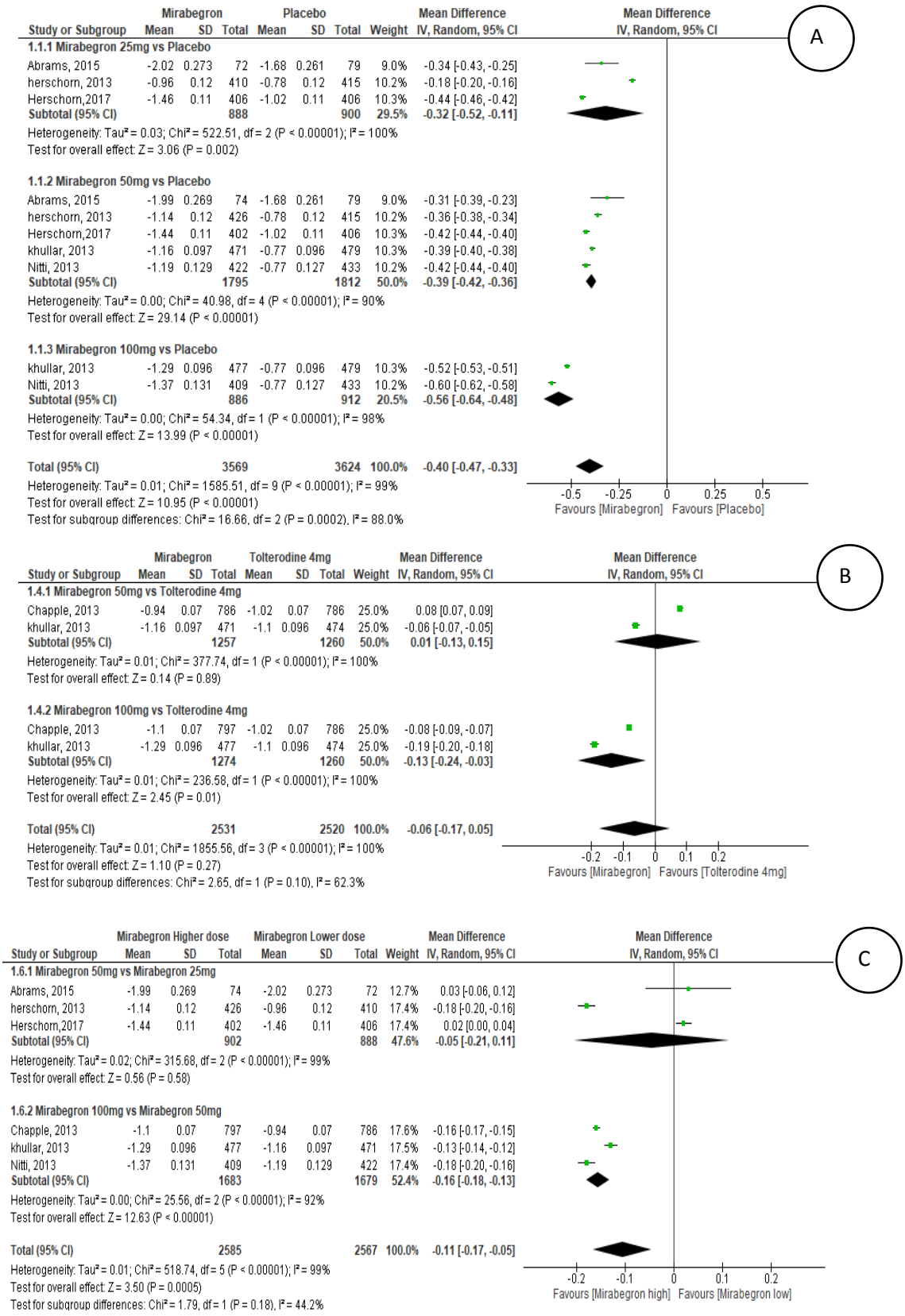

Fig. 3. Micturition/24hours comparison of mirabegron with (A) Placebo, (B) Tolterodine, (C) different doses of mirabegron

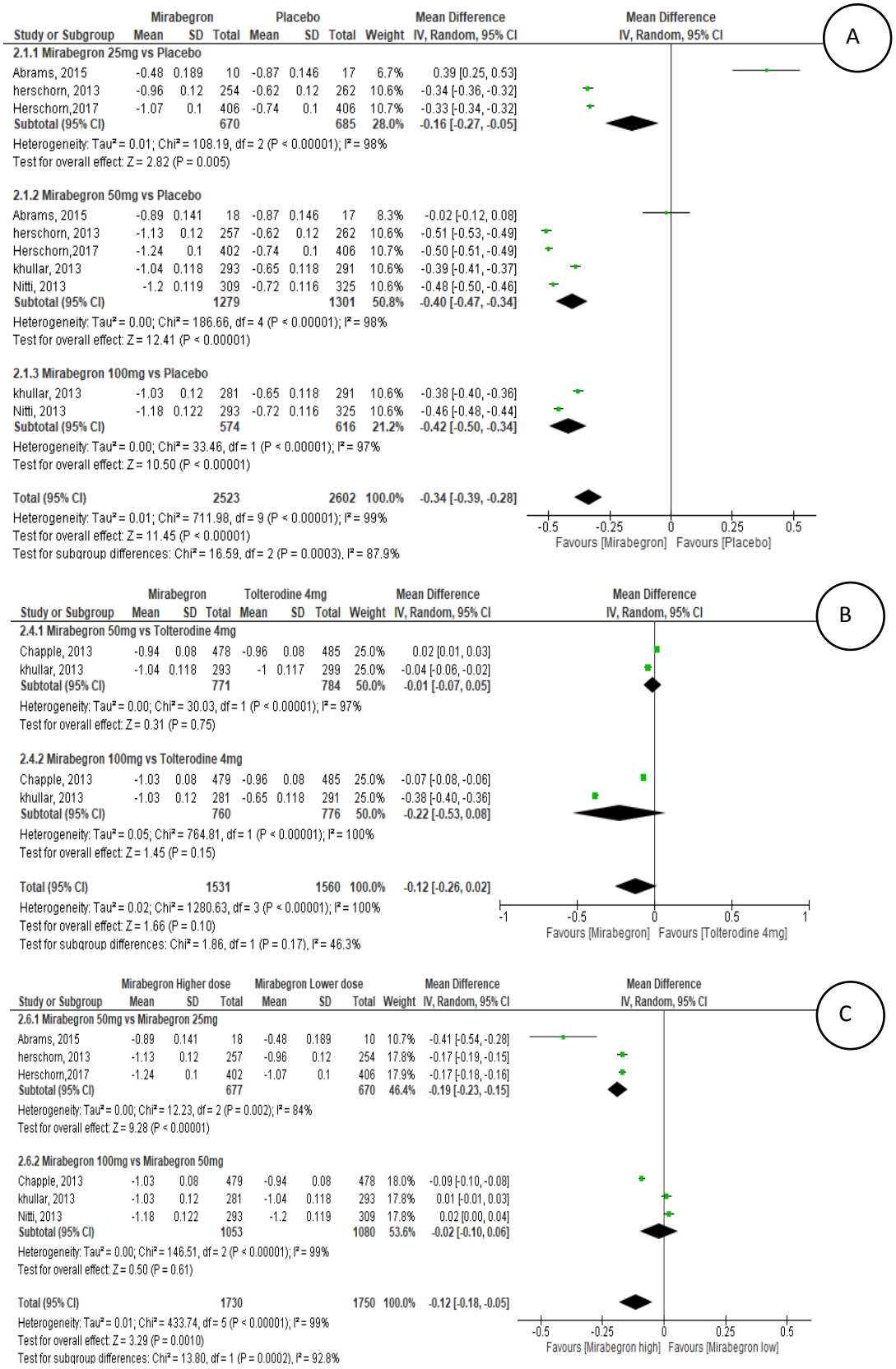

Fig. 4. Incontinence episode/24hours comparison of mirabegron with (A) Placebo, (B) tolterodine, (C) different doses of mirabegron

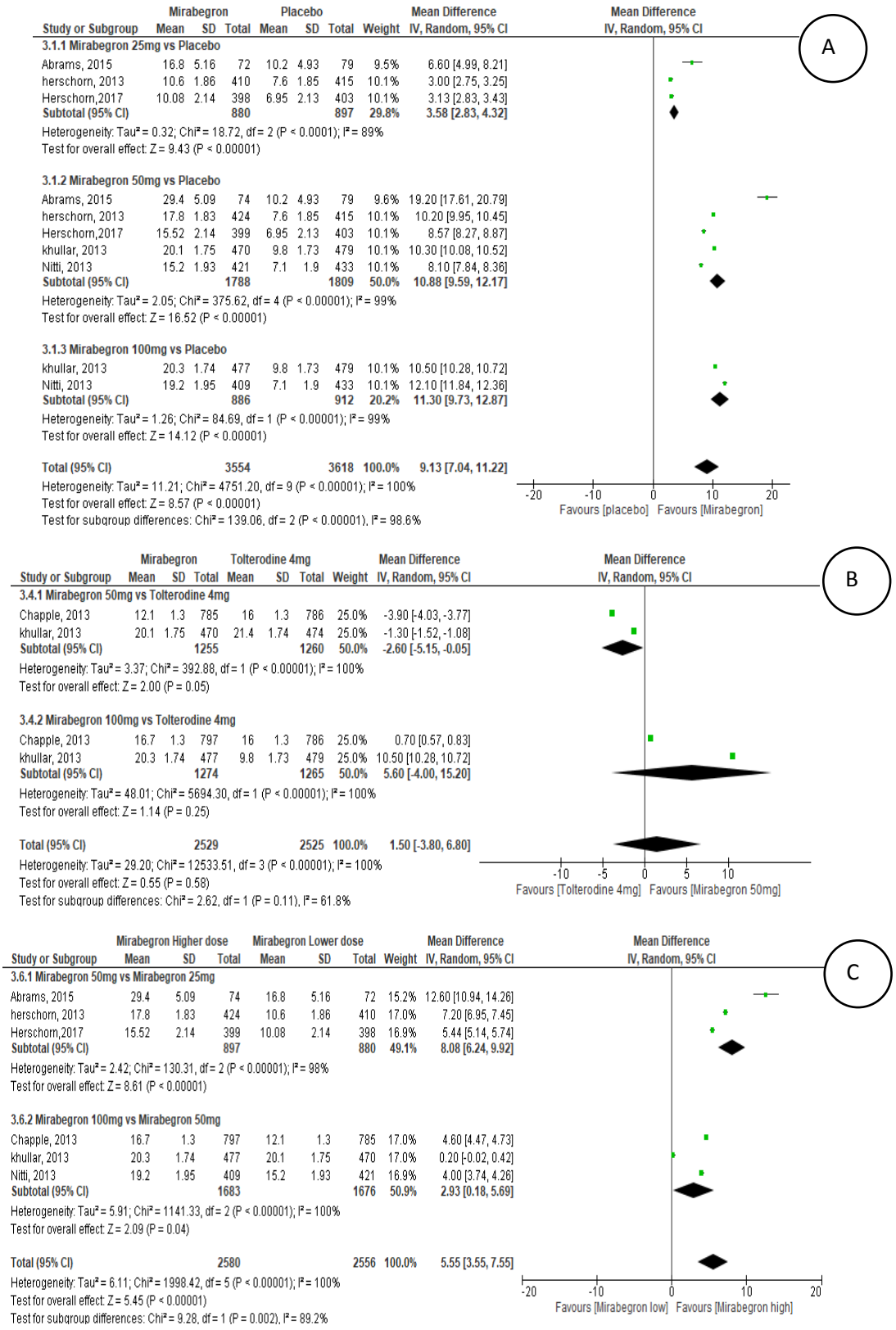

Fig. 5. Mean Volume Voided/micturition comparison of mirabegron with (A) placebo, (B) tolterodine, (C) different doses of mirabegron

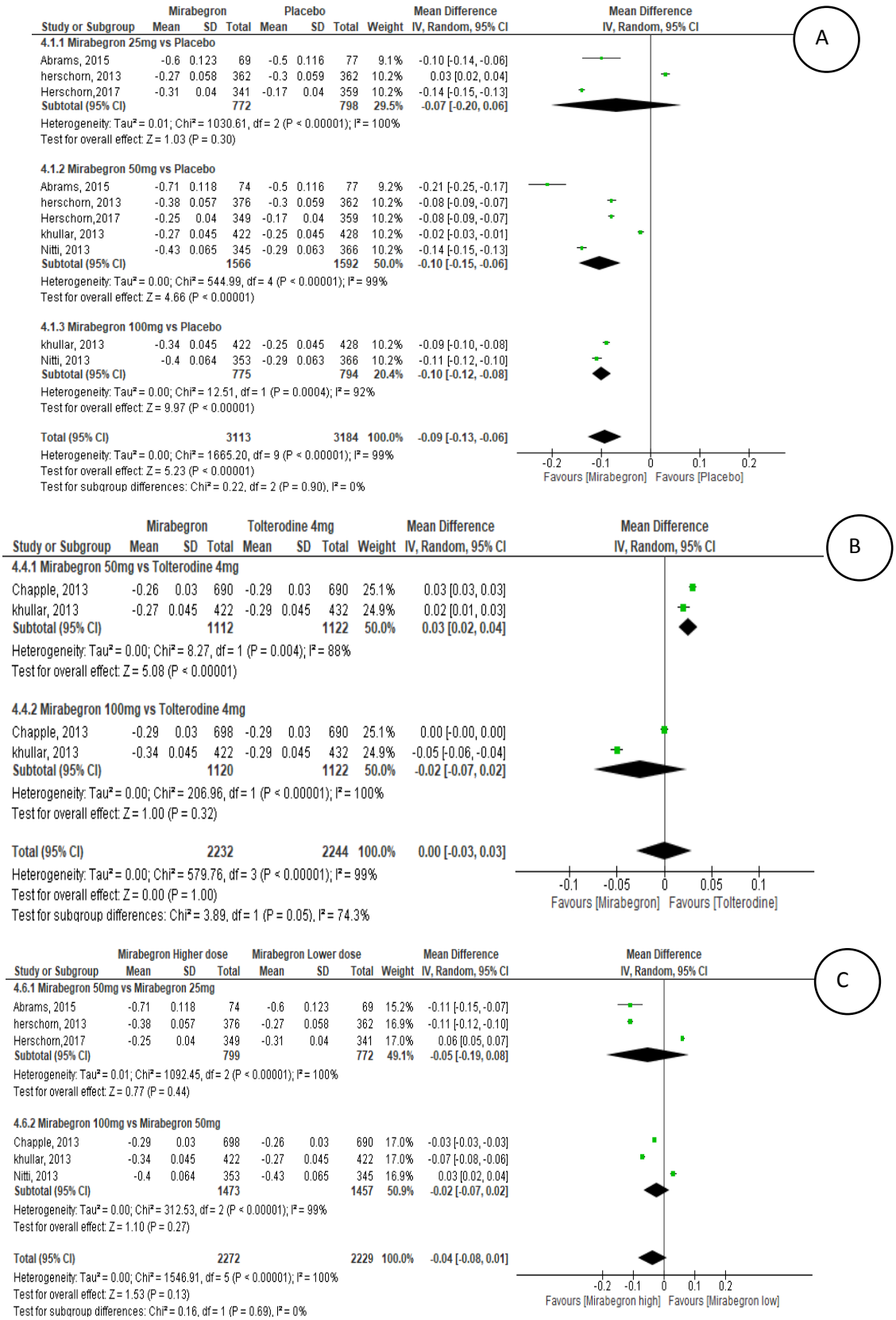

Fig. 6. Nocturia episode/24 hours comparison of mirabegron with (A) Placebo, (B) tolterodine, (C) different doses of mirabegron

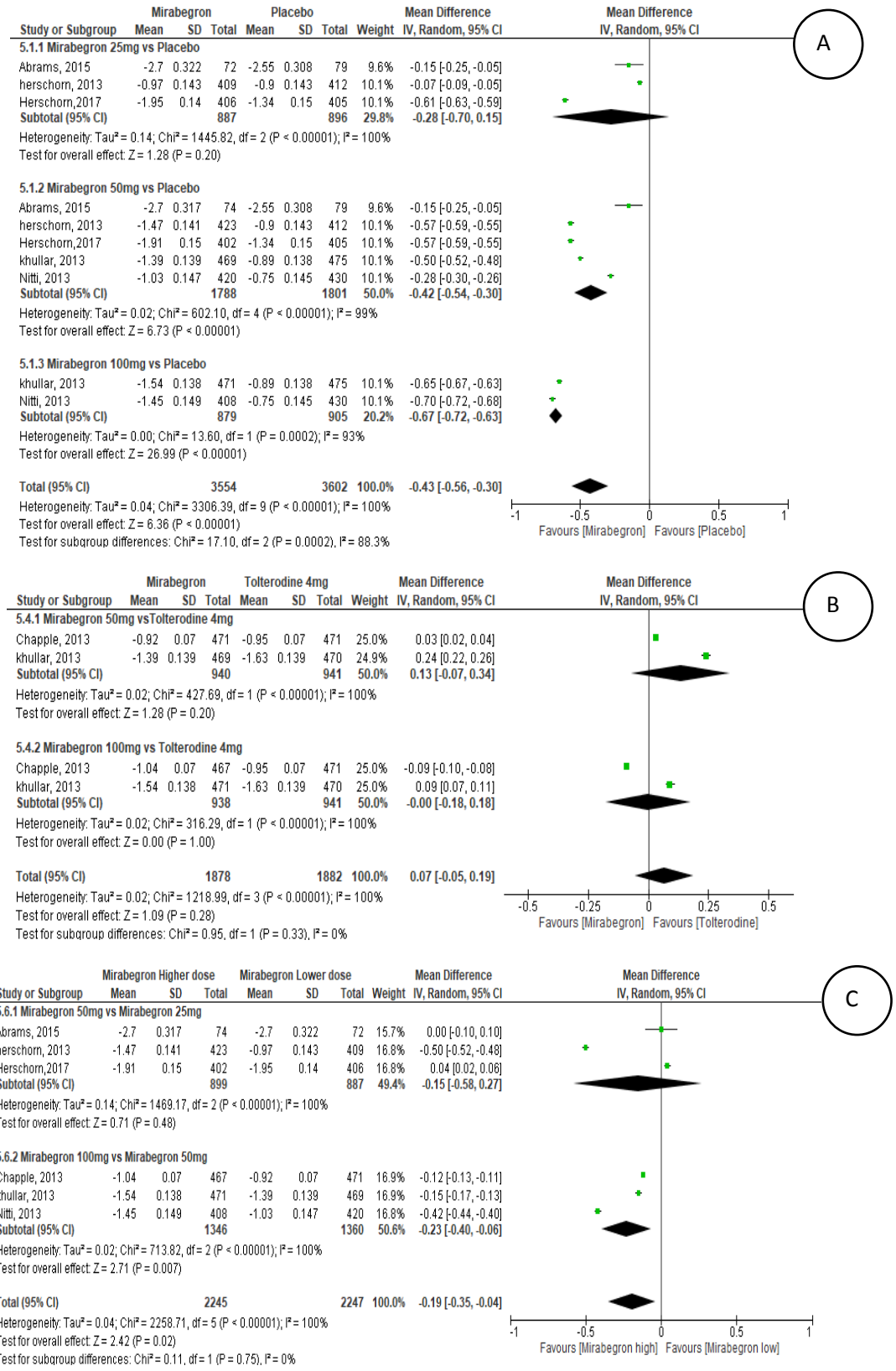

Fig. 7. Urgency Episode/24 hours comparison of mirabegron with (A) placebo, (B) tolterodine, (C) different doses of mirabegron

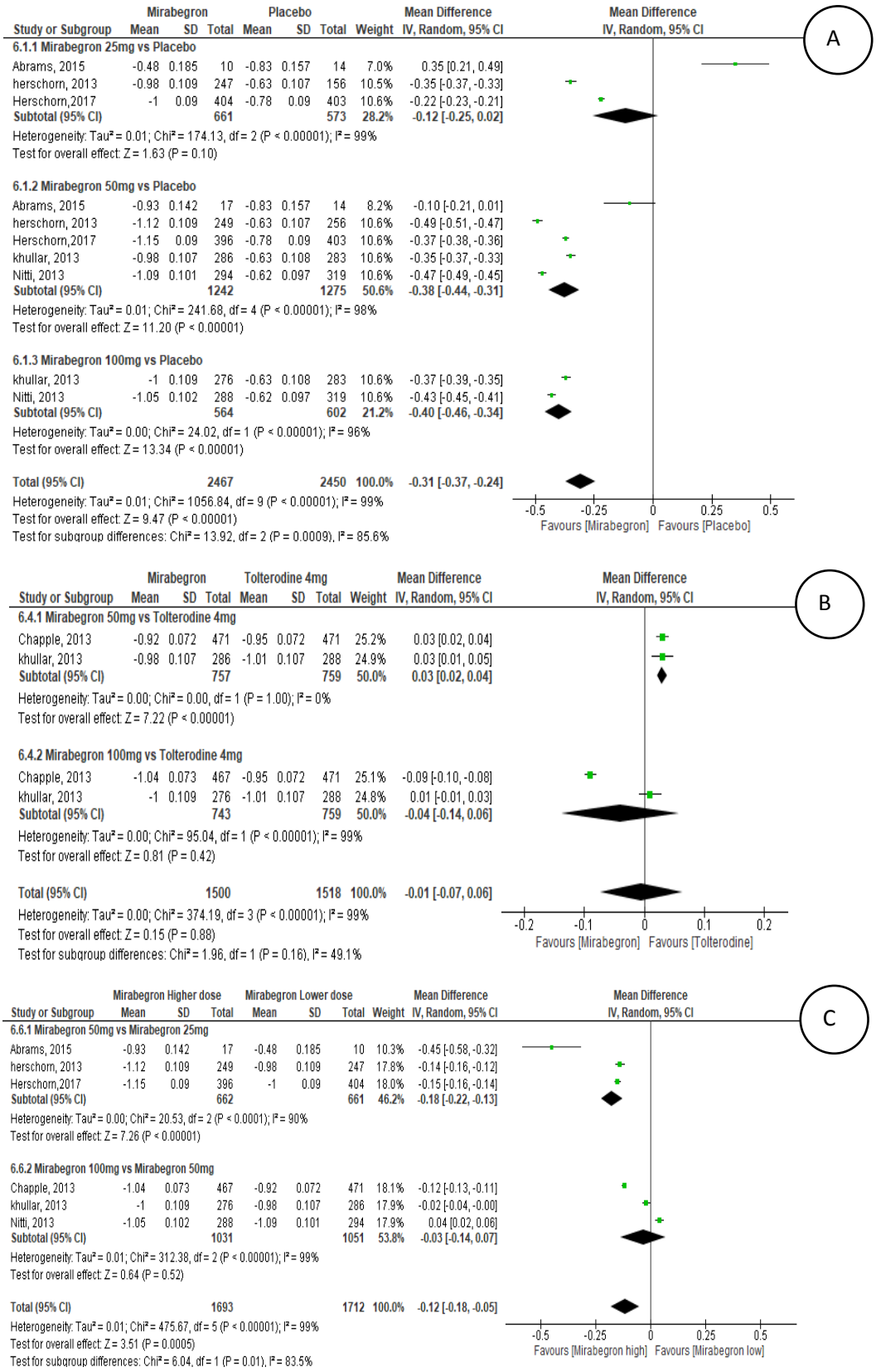

Fig. 8. Urgency incontinence episode/24 hours comparison of mirabegron with (A) placebo, (B) tolterodine, (C) different doses of mirabegron

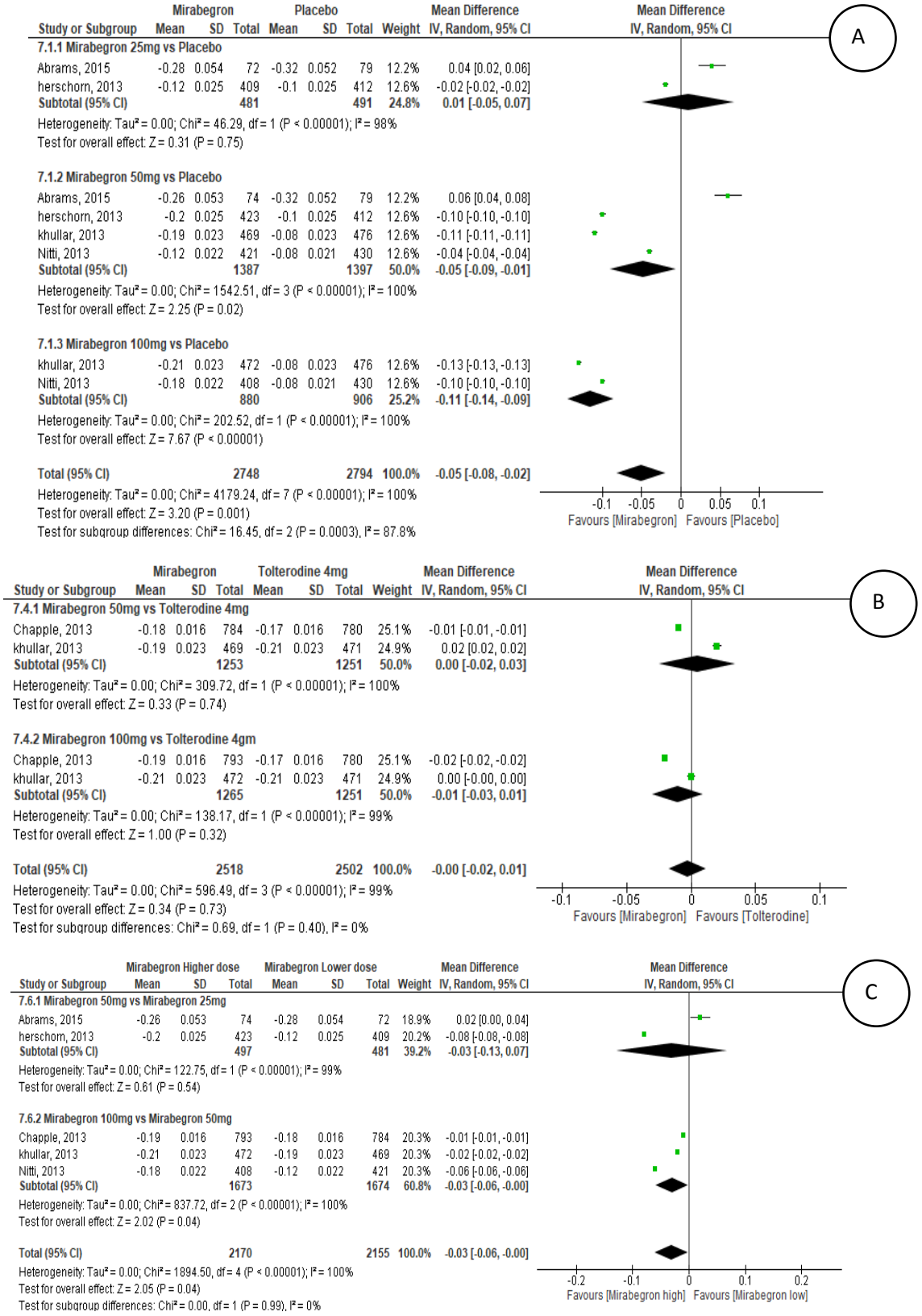

Fig. 9. Level of urgency (Grade 3 or 4)/24 hours comparison of mirabegron with (A) placebo, (B) tolterodine, (C) different doses of mirabegron

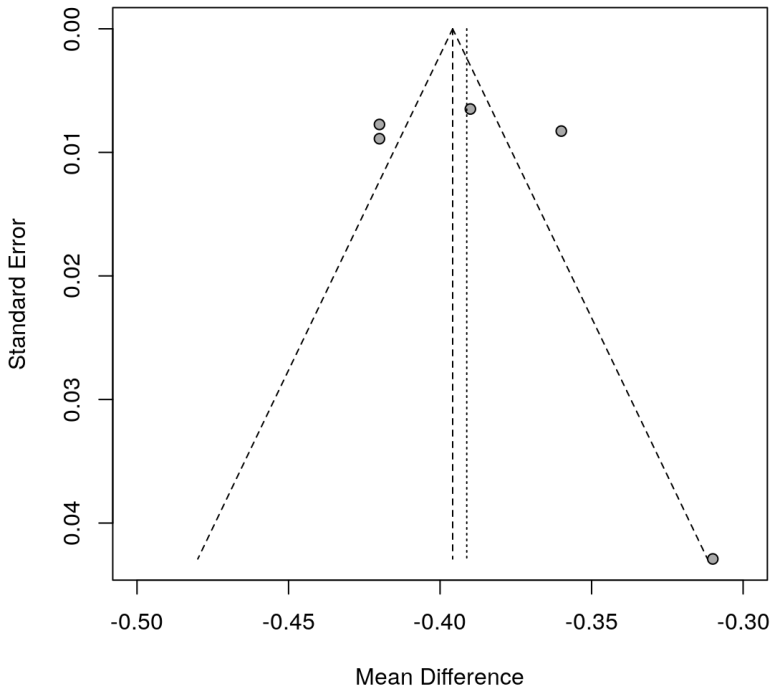

Fig. 10. Funnel plot of the included studies

4. DISCUSSION

OAB is defined as "urinary urgency, usually accompanied by frequency and nocturia, with or without urge urinary incontinence" [12]. There are various modalities of treatment that can be used in patients with overactive bladder. The current pharmacological treatment guideline for OAB was using anticholinergic (antimuscarinics) drugs.[1]However, despite their efficacy, antimuscarinics also have a high rate of side effects during long-term treatment, particularly in the elderly population. Thus, the use of alternative treatment needs to be considered, including botulinum toxin injections, posterior tibial nerve neuromodulator, sacral neuromodulator and the use of β adrenergic agents [1,12]. Tolerability, treatment duration, and cost are often the deciding points for patient choice and compliance.

A study conducted by Yamaguchi et al. in 2014 concluded that the use of mirabegron evaluated within three months of treatment was good and safe in terms of efficacy and side effects. The effect of mirabegron is also said to be dose-dependent on the criteria of all the assessment variables. Although on the contrary, the most satisfying results for micturition frequency/24 hours' dose was obtained from mirabegron 50 mg [13]. Different results were found from the study of Chapple et al. in 2019, where three types of drugs and five comparisons were carried out. The research results concluded that mirabegron gave better results than placebo from all research variables and was dose-dependent (except for the incontinence episode/24 hours variable). In addition, mirabegron was also found to give better results than tolterodine but still lower than solifenacin. In terms of side effect assessment, mirabegron was superior to other antimuscarinics in dry mouth and had similar results for other variables [14].

Three meta-analyses have been conducted comparing the efficacy and safety of Mirabegron for OAB treatment. Cui et al. analyzed four studies that compared the efficacy and safety of Mirabegron and placebo over three months [15]. Wu et al. analyzed six studies that compared the same aspect as a prior study for mirabegron, tolterodine and placebo [16]. The latest one is Arcangelo et al., which evaluated eight studies up to May 2016 evaluates the safety and efficacy of different doses of Mirabegron in the treatment of OAB by comparing the number of episodes of incontinence per 24 hours, mean volume voided per micturition from mirabegron 50 mg, mirabegron 100 mg, and tolterodine 4 mg. It also reports the risk of treatment-emergent after effect (TEAE) between each drug and placebo from baseline to 12 weeks of treatment. However,

prior studies haven't analyzed urgency incontinence per 24 hours and the level of urgency aspect of Mirabegron [17].

From the result of this study, we found that within four weeks' follow-up period, Mirabegron has shown better efficacy compared with placebo in improving all seven criteria used to assess efficacy (including the mean number of micturition/day, mean incontinence episodes/day, mean micturition volume voided/micturition, mean nocturia micturition/day, mean urgency episodes/day, mean urgency incontinence episodes/day and mean level of urgency [grade 3 or 4]/day). We also found that, the lowest dose treatment obtained from mirabegron 25 mg can already provide significant results compared to placebo within 4 weeks' range of treatment. In contrast, the comparison of mirabegron with tolterodine 4 mg showed no significant difference in outcome across all seven assessment criteria at a 4-weeks' follow-up.

A meta-analysis study conducted previously by Sebastianelli et al. in 2017 concluded that mirabegron provides superior results compared to tolterodine. The research was carried out using a time span of 3 months as a reference for assessment. However, from the forest plot results, it appears that mirabegron and tolterodine did not have a significant difference in results from several variables assessed [17]. Another meta-analysis study conducted by Wu et al. in 2014 gave similar results where mirabegron gave better results than placebo and tolterodine on incontinence episode variables. Still, no significant difference was found in tolterodine comparison on other variables [16] all of these results concluded that the comparison of mirabegron with tolterodine was not significantly different in efficacy at the beginning of 4 weeks of treatment, but further treatment could give different results. On the other hand, the comparison of mirabegron with different doses of mirabegron showed significant results at higher doses assessed from all assessment criteria except for mean nocturia episodes per day criteria, where there was no significant difference between the two doses.

To our knowledge, this is the first study to use a 4-weeks' time span as a reference for assessing the efficacy of mirabegron. However, due to this, there are several shortcomings in this study, including the limitations of research data where not all RCTs have detailed follow-up data within four weeks so that assessment of several variables of efficacy, tolerability and side effects of drugs cannot be carried out (despite our efforts to contact the authors and get the original data). Although to the best of our effort to include all relevant studies (both published and non-published), this study does not include un-published research (thesis or dissertation), and the included studies were relatively a few. As the funnel plot previously illustrate, we could not reject any possibility of publication bias. Nevertheless, these aforementioned shortcomings can affect the results of this metanalysis when new studies published, another round of analysis might needed to obtain a more accurate conclusion.

5. CONCLUSION

From the results of this study, it can be concluded that in a 4-week treatment range, Mirabegron can provide significant results compared to placebo. However, the results are still not much different from tolterodine. Higher doses of mirabegron also provide a better result when compared with lower doses. The lowest dose with statistically significant results compared to placebo was obtained from mirabegron 25 mg. Further treatment within three months or more can provide changes to each drug's result and the side effect profile. Additional research to see the side effects of the drug is still needed to confirm the best dose with minimal side effects and significant results.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Leron E, Weintraub AY, Mastrolia SA, Schwarzman P. Overactive bladder syndrome : Evaluation and management. 2018;117–25.
2. Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, et al. A comprehensive review of overactive

bladder pathophysiology: On the way to tailored treatment (Figure presented.). Eur Urol. 2019;75(6):988–1000.
3. Eapen RS, Radomski SB. Review of the epidemiology of overactive bladder. Res Reports Urol. 2016;8:71–6.
4. Chuang YC, Liu SP, Lee KS, Liao L, Wang J, Yoo TK, et al. Prevalence of overactive bladder in China, Taiwan and South Korea: Results from a cross-sectional, population-based study. LUTS Low Urin Tract Symptoms. 2019;11(1):48–55.
5. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (Non-Neurogenic) in adults: AUA/SUFU guideline amendment 2019. J Urol. 2019;202(6 SUPPL.):558.
6. Wang CL, Wu CH, Liu CM, Shen CJ, Lin KL, Long CY. Clinical and urodynamic effects of tolterodine in women with an overactive bladder. Taiwan J Obstet Gynecol. 2013;52(3):381–4.
7. Shen YC, Wang HJ, Chuang YC. Efficacy and persistence of low-doses mirabegron (25 mg) in patients with overactive bladder: Analysis in a real-world urological practice. Int Urol Nephrol. 2018;50(7):1219–26.
8. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F, et al. Persistence and adherence with mirabegron versus antimuscarinic agents in patients with overactive bladder: A retrospective observational study in UK clinical practice. Eur Urol. 2017;72(3):389–99.
9. Sussman D, Yehoshua A, Kowalski J, Lee W, Kish J, Chaudhari S, et al. Adherence and persistence of mirabegron and anticholinergic therapies in patients with overactive bladder: a real-world claims data analysis. Int J Clin Pract. 2017;71(3–4):1–8.
10. Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, et al. Efficacy and tolerability of mirabegron, a β3-adrenoceptor agonist, in patients with overactive bladder: Results from a randomised European-Australian phase 3 trial. Eur Urol. 2013;63(2):283–95.
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372.
12. Willis-Gray MG, Dieter AA, Geller EJ. Evaluation and management of overactive bladder: Strategies for optimizing care. Res Reports Urol. 2016;8:113–22.
13. Yamaguchi O, Marui E, Igawa Y, Takeda M, Nishizawa O, Ikeda Y, et al. Efficacy and safety of the selective β3-adrenoceptor agonist mirabegron in japanese patients with overactive bladder: A randomized, double-blind, placebo-controlled, doses-finding study. LUTS Low Urin Tract Symptoms. 2015;7(2):84–92.
14. Chapple CR, Cruz F, Cardozo L, Staskin D, Herschorn S, Choudhury N, et al. Safety and efficacy of mirabegron: Analysis of a large integrated clinical trial database of patients with overactive bladder receiving mirabegron, antimuscarinics, or placebo[Formula presented]. Eur Urol. 2020;77(1):119–28.
15. Cui Y, Zong H, Yang C, Yan H, Zhang Y. The efficacy and safety of mirabegron in treating OAB: A systematic review and meta-analysis of phase III trials. Int Urol Nephrol. 2014;46(1):275–84.
16. Wu T, Duan X, Cao CX, Peng C Du, Bu SY, Wang KJ. The role of mirabegron in overactive bladder: A systematic review and meta-analysis. Urol Int. 2014;93(3):326–37.
17. Sebastianelli A, Russo GI, Kaplan SA, McVary KT, Moncada I, Gravas S, et al. Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive bladder: Comparison with placebo and tolterodine. Int J Urol. 2018;25(3): 196–205.

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