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Safety and efficacy of beta-3 adrenergic agonists in treating neurogenic lower urinary tract dysfunction: A systematic review and meta-analysis

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Purpose: To evaluate efficacy and safety of beta-3 adrenergic agonists in adults with neurogenic lower urinary tract dysfunction.

Materials and Methods: According to a protocol (CRD42022350079), we searched multiple data sources for published and unpublished randomized controlled trials (RCTs) up to 2nd August 2022. Two review authors independently screened studies and abstracted data from the included studies. We performed statistical analyses by using a random-effects model and interpreted them according to the Cochrane Handbook for Systematic Reviews of Interventions. We used GRADE guidance to rate the certainty of evidence (CoE).

Results: We found data to inform two comparisons: beta-3 adrenergic agonists versus placebo (4 RCTs) and anticholinergics (2 RCTs). Only mirabegron was used for intervention in all included studies. Compared to placebo, beta-3 adrenergic agonists may have a clinically unimportant effect on urinary symptoms score (mean difference [MD] -2.50, 95% confidence interval [CI] -4.78 to -0.22; I^2=92%; 2 RCTs; 192 participants; low CoE) based on minimal clinically important difference of 3. We are very uncertain of the effects of beta-3 adrenergic agonists on quality of life (MD 10.86, 95% CI 1.21 to 20.50; I^2=41%; 2 RCTs; 98 participants; very low CoE). Beta-3 adrenergic agonists may result in little to no difference in major adverse events (cardiovascular adverse events) (risk ratio 0.57, 95% CI 0.14 to 2.37; I^2=0%; 4 RCTs; 310 participants; low CoE). Compared to anticholinergics, no study reported urinary symptom scores and quality of life. There were no major adverse events (cardiovascular adverse events) in either study group (1 study; 60 participants; very low CoE).

Conclusions: Compared to placebo, beta-3 adrenergic agonists may have similar effects on urinary symptom scores and major adverse events. There were uncertainties about their effects on quality of life. Compared to anticholinergics, we are either very uncertain or have no evidence about urinary symptom scores, quality of life, and major adverse events.

Keywords: Adrenergic beta-3 receptor agonists; Neurogenic bladder; Systematic review

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INTRODUCTION

The lower urinary tract (LUT) has two main functions: urine storage and bladder emptying. This depends on multiple coordinated neurological levels, that require an intact central and peripheral nervous system. Therefore, neurogenic lower urinary tract dysfunction (NLUTD), which results from any neurological disease, leads to dysfunction in bladder storage and/or emptying, depending on the location of the neurological insult [1].

NULTD patients are at high risk for recurrent urinary tract infections, urinary incontinence, vesicoureteral reflux, and renal impairment. Therefore, they require lifelong, intensive medical care to deal with these complications, improve their quality of life (QOL), and maximize their life expectancy [2,3].

Anticholinergic agents are the first-line treatment for storage symptoms in NLUTD patients. Nevertheless, these drugs come with undesirable adverse events such as dry mouth, constipation, voiding difficulty or acute urine retention, and potentially cognitive impairment [4,5]. Therefore, to avoid these adverse effects, a novel, effective, and safe therapeutic agents are needed.

The human bladder contains three subtypes of beta-adrenergic receptors (beta-1, beta-2, and beta-3), with 97% being beta-3. Activation of beta-3 receptors result in detrusor muscle relaxation. Therefore, detrusor overactivity can be managed effectively by targeting these receptors [6-8]. Unfortunately, many early agents targeting these receptors had significant cardiac side effects. However, mirabegron which is a selective beta-3 adrenergic agonist is now in clinical use and is an effective treatment for idiopathic detrusor overactivity. Its receptor specificity leads to very low side effects and a better safety profile than anticholinergic drugs [9,10]. In addition, a new beta-3 adrenergic agonist, vibegron, has been developed and approved in Japan, and clinical trials for new beta-3 adrenergic agonist molecules are ongoing.

The American Urological Association has recommended mirabegron as a grade C level of evidence for NLUTD management, based on one systematic review of seven studies [11]. Similarly, the European Association of Urology guidelines stated that mirabegron's role in NLUTD is unclear [5].

Therefore, we performed our systematic review and meta-analysis to assess the efficacy and safety of beta-3 adrenergic agonists as a treatment for NLUTD patients and ensure a feasible reference for clinical practice.

MATERIALS AND METHODS

After registration in the International Prospective Register of Systematic Reviews database (CRD42022350079), a systematic review was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12,13].

We performed a comprehensive search including MEDLINE, Embase, Cochrane Library, Scopus, Web of Science, Latin America and the Caribbean Literature on Health Sciences, World Health Organization, Canadian Agency for Drugs and Technologies in Health, grey literature, ClinicalTrials.gov, and hand search with no restrictions on the language of publication or publication status up to 2nd August 2022. Full details of the search strategies were reported in supplementary file (Supplementary Material).

1. PICOs (participants, intervention, comparator, outcome, study design)

1) Participants

Adult patients with NLUTD from any neurologic disorders

2) Interventions

Beta-3 adrenergic agonists tested in clinical trials: mirabegron, ritobegron, solabegron, and vibegron

3) Comparisons

- Beta-3 adrenergic agonists versus placebo
- Beta-3 adrenergic agonists versus anticholinergics

4) Outcomes

Primary outcomes were the change from the baseline in the urinary symptoms score using validated questionnaires, such as overactive bladder symptoms score (OABSS) and overactive bladder questionnaire short form (OAB-q SF), the QOL using Incontinence Quality of Life (I-QOL) questionnaire or International Consultation on Incontinence Questionnaire (ICIQ) and major adverse events which are cardiovascular side effects.

Secondary outcomes were complications due to neurogenic disease, such as urinary tract infection and renal insufficiency, overall adverse events, acute urinary retention, and changes of voiding diary (e.g., number of micturitions per day, number of urgency episodes per day).

We considered outcomes measured up to and including 12 months after randomization as short term, and beyond 12 months as long term.

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5) Study design

Randomized controlled trial (RCT)

2. Assessment of risk of bias in included studies

Two review authors assessed the risk of bias of each included study independently using Cochrane's 'Risk of bias' assessment tool 2.0. We resolved disagreements by consensus, or by consultation with a third review author.

We judged risk of bias domains as 'low risk', 'high risk', or 'some concerns', and we evaluated individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions [14].

3. Data collection and analysis

We performed statistical analyses using random-effects model according to the statistical guidelines contained in the Cochrane Handbook for Systematic Reviews of Interventions. We interpreted random-effects meta-analyses with due consideration of the whole distribution of effects. For dichotomous outcomes, we used the Mantel–Haenszel method; for continuous outcomes, we used the inverse variance method; we used risk ratio (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes. We used Review Manager 5 software to perform analyses (RevMan 2014) (The Cochrane Collaboration) [15].

We expected characteristics, such as age (age more than 65 years vs. age less than 65 years), sex, symptom severity according to OABSS, and neurogenic disease type (suprasacral spinal cord disease and suprapontine disease) to introduce clinical heterogeneity, and planned to carry out subgroup analyses with investigation of interactions. The I^2 is used as an indicator to assess heterogeneity. I^2 values of 25%, 50%, and 75% generally denote a small, moderate, and a high proportion of variability, respectively. We performed sensitivity analysis excluding studies rated as unclear or high risk of bias.

4. Summary of findings table

Two review authors independently rated the certainty of evidence (CoE) for each outcome, and any discrepancies were resolved by consensus or by consultation with a third review author. For the included studies, we considered criteria related to internal validity (risk of bias, inconsistency, imprecision, and publication bias), as well as external validity, such as the directness of results [16,17].

We rated the CoE according to the GRADE approach using a minimally contextualized approach with predefined thresholds for minimally clinically important differences [18,19].

RESULTS

1. Search results

We classified studies using reference management software (EndNote; Clarivate) and Rayyan (https://www.rayyan.ai/) and extracted data from the included studies. We resolved discrepancies through consensus or recourse to a third review author.

A search of electronic databases yielded 335 records. Following the removal of duplicates, we screened the titles and abstracts of 218 records and excluded 203. We screened 15 full-text articles, and excluded 9 studies that did not meet the inclusion criteria. Seven studies were non randomized study [20-26] and 2 studies included a wrong population (i.e., patients with idiopathic detrusor overactivity) [27,28]. The assessment process is illustrated in the PRISMA flowchart (Fig. 1) [29].

2. Included studies

We included a total of 6 studies in the review and all of them were published in English as shown in Table 1. The included studies were conducted in Korea [30], Greece [31], Czech Republic [32], Lebanon [33], Canada [34], and India [35]. Among six included studies, we contacted the corresponding authors of five studies for additional information on the results and received replies for four [30,32,34,35].

The studies included adult patients with neurogenic detrusor overactivity due to multiple sclerosis, spinal cord injury, cerebrovascular accident, and parkinsonism. Only mirabegron was used for intervention in all included studies. Four agents, namely placebo and anticholinergics (solifenacin, fesoterodine, darifenacin) were used as comparators. The comparisons in four and two studies were mirabegron versus placebos [30,32-34] and mirabegron versus anticholinergics [31,35], respectively. Follow-up ranged from 6 to 12 weeks. Regarding outcomes, two studies reported the improvement in symptoms using OABSS [30,33]. The QOL was assessed in two studies using I-QOL [32,34]. Major adverse events (cardiovascular adverse events), overall adverse events, and acute urine retention were reported in 5 studies [30,32-35]. Any included studies did not report complications associated with neurogenic disease.

Two studies reported funding from pharmaceutical companies [30,34]. The other 4 studies reported no conflict of interests.

3. Effects of intervention

We included 6 RCTs with 461 adult patients with NLUTD. Four studies compared mirabegron with placebos

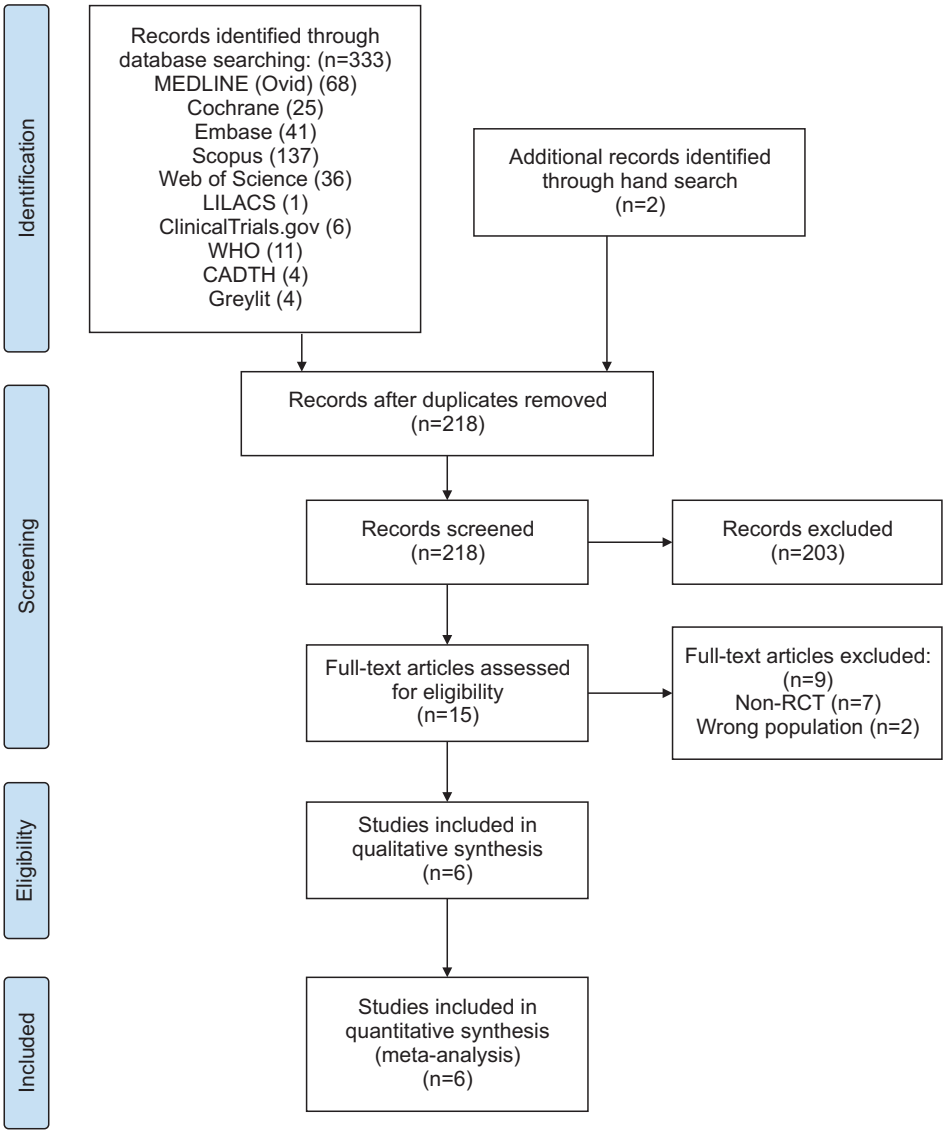

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. LILACS, Latin America and the Caribbean Literature on Health Sciences; WHO, World Health Organization; CADTH, Canadian Agency for Drugs and Technologies in Health; RCT, randomized controlled trial.

and 2 studies compared mirabegron with anticholinergics (Tables 2, 3). The forest plots for each analysis were presented as supplementary file (Supplementary Figs. 1-7).

1) Beta-3 adrenergic agonists versus placebo

(1) Primary outcomes

A. Urinary symptoms score: Two studies comparing beta-3 adrenergic agonists versus placebo reported change from the baseline in the symptoms score using OABSS, beta-3 adrenergic agonists may have a trivial (clinically unimportant) effect on urinary symptom scores (MD -2.50, 95% confidence interval [CI] -4.78 to -0.22; I^2=92%; 2 RCTs; 192 participants; low CoE) (Supplementary Fig. 1) [30,33].

B. Quality of life: The two studies used I-QOL questionnaire [32,34] to assess QOL. We are very uncertain about the effects of beta-3 adrenergic agonists on QOL (MD 10.86, 95% CI 1.21 to 20.50; I^2=41%; 2 RCTs; 98 participants; very low CoE) (Supplementary Fig. 2) [32,34].

C. Major adverse events (cardiovascular side effects): Beta-3 adrenergic agonists may result in little to no difference in major adverse events (cardiovascular side effects) (RR 0.57, 95% CI 0.14 to 2.37; I^2=0%; 4 RCTs; 310 participants; low CoE) [30,32-34]. This would correspond to 14 fewer major adverse events per 1,000 patients (95% CI 28 fewer to 45 more) (Supplementary Fig. 3).

(2) Secondary outcomes

A. Complications due to neurogenic disease: No study reported this outcome.

B. Overall adverse events: We are very uncertain about the effects of beta-3 adrenergic agonists on overall adverse events (RR 0.88, 95% CI 0.57 to 1.35; I^2=0%; 4 RCTs; 310 participants; very low CoE) [30,32-34]. This would correspond to 26 fewer adverse events per 1,000 patients (95% CI 94 fewer

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Table 1. Baseline characteristics of the included studies

Study	Country/ settings/ design	Inclusion criteria	Intervention/dose		No. of participants (experimental/ control)	Outcome	Duration (wk)	Results
			Experimental	Control				
Cho et al. [30] (2021)	Korea/ multicenter/ RCT	Patients >20 years old who were diagnosed with parkinsonism with OAB symptoms for >4 weeks, OABSS questionnaire scores greater than 2, and OABSS urgency question scores greater than 1	Mirabegron 50 mg	Placebo	58/59	1. Primary outcome is the change in the total OABSS. 2. Secondary outcomes are the change in voiding dairy parameters, IPSS score, post voiding residual volume, treatment satisfaction using TSQ, PPBC, and GRA.	12	1. The OABSS scores were significantly different between the two groups in favor of mirabegron after 8 weeks, OABSS for placebo was 7.74±2.80 and for mirabegron 6.47±3.05 (p=0.035). 2. Voiding dairy parameters, IPSS scores, and treatment satisfaction scores not significantly different between the two groups.
Glykas et al. [31] (2021)	Greece/ multicenter/ RCT	MS patients >18 years old diagnosed with LUTD	Mirabegron 25 or 50 mg	Solifenacin 5 mg or 10/ fesoterodine 4 mg or 8 mg	46/45	1. Primary outcomes is symptom improvement between patients treated with B3 agonists and anticholinergics using MusiQoL and NBSS questionnaires. 2. Secondary outcomes are calyceal or pelvic dilatations in ultrasounds, PVR, urine cultures and the urination diaries data between the two groups at first visit and 3 months after treatment.	12	1. Both groups showed a significant improvement in symptoms after treatment; however, no statistical difference was noted between the mirabegron group and the anticholinergic group in terms of symptoms improvement as assessed by NBSS, NBSS for anticholinergic group was 19.9 and was in mirabegron group 20.1 (p=0.24) and MusiQoL for anticholinergic group was 47.6 and was in mirabegron group 50.5 (p=0.4). 2. No difference from their baseline in terms of PVR for (p=0.28), upper tract dilatations (p=0.5), urine cultures (p=0.5), and urination dairies which included dairy urgency episodes (p=0.078) and dairy number of urinations (p=0.43) between patients treated either with mirabegron or anticholinergics.
Krhut et al. [32] (2018)	Czech/ multicenter/ RCT	Individuals 18–65 years old with NDO due to SCI or MS	Mirabegron 50 mg	Placebo	32/34	1. Primary endpoint is the change from baseline in cystometric capacity. 2. The secondary endpoints are changes from baseline in urodynamic variables (volume at first detrusor contraction, compliance, and maximal detrusor pressure), the severity of incontinence (as measured by pad-weight test), patient-reported outcomes (as measured by PPBC scale, I-QOL questionnaire, and treatment satisfaction-VAS) and safety variables.	6	1. Cystometric capacity increased in mirabegron group but not reached statistically significant difference, in mirabegron group cystomtric capacity increased from 183.5 to 238.81 mL after treatment, and in placebo group decreased from 210.4 to 167.56 mL (p=0.061). 2. There was a significant improvement in volume at first detrusor contraction (p=0.0005) and compliance (p=0.0041) in mirabegron group. 3. No significant change in maximal detrusor pressure between both groups (p=0.3173). 4. There was an improvement of urine leakage in mirabegron group but not reached statistically significant difference (p=0.056). 5. There were statistically significant differences in all the patient-reported outcomes in favor of mirabegron which were assessed by PPBC (p=0.0013), I-QOL (p=0.006), and treatment satisfaction-VAS (p=0.00045). 6. There were no statistically significant changes in any safety variable in either group from baseline until the end of the treatment period.

Table 1. Continued

Study	Country/ settings/ design	Inclusion criteria	Intervention/dose		No. of participants (experimental/ control)	Outcome	Duration (wk)	Results
			Experimental	Control				
Moussa et al. [33] (2022)	Lebanon/single center/RCT	Patients 40–70 years old who were diagnosed with parkinsonism with urgency score of >2 and a total score of >3 on the OABSS	Mirabegron 50 mg	Placebo	53/42	1. Primary outcome is the change from baseline in OABSS, OAB-q SF score. 2. Secondary outcome is the change from baseline in voiding dairy parameters.	12	1. There was a significant improvement in the primary outcome as assessed by OABSS. OABSS in the mirabegron group decreased from 10.2±1.2 to 6.9±1.4 (p<0.001) and in the placebo group decreased from 10.7±1 to 10.5±1.1 (p=0.03) moreover after treatment 72% of mirabegron group reached MCID for OABSS compared to 0% in the placebo group (p<0.001), OAB-q SF in mirabegron group decreased from 39.8±8.1 to 22.2±7.4 (p<0.001) and in placebo group decreased from 51.3±7.7 to 48.7±12 (p=0.2). 2. There was a significant improvement in secondary outcome measures in the treatment group compared to the placebo group. In the treatment group, the mean number of micturition episodes/24 h decreased significantly from baseline to the end of treatment (from 11 to 8.7, respectively, p<0.001), also the mean number of micturition/night, the mean number of urgency episodes/24 h and the mean number of leaks/24 h decreased significantly from baseline to the end of treatment (from 1.5±0.6 to 1.1±0.7; from 2.4±1.1 to 0.6±0.6; and from 2.2±1.2 to 0.4±0.6, respectively, p<0.001). In the placebo group, all bladder diary parameters remained almost the same and did not reach any statistically significant differences between baseline and week 12 of the trial.
Welk et al. [34] (2018)	Canada/ multicenter/ RCT	Individuals >18 years of age with either a non-acute SCI or MS, and bothersome urinary symptoms (frequency, urgency, urgency incontinence) and at least one episode of urgency/unaware incontinence during the 3-day voiding diary	Mirabegron 50 mg	Placebo	16/16	1. Primary urodynamic outcome is maximum cystometric capacity. 2. Secondary urodynamic outcomes are the presence of NDO, peak pressure of NDO, and volume at first NDO. 3. Additional efficacy outcomes included changes in functional bladder capacity, urinary frequency, and incontinence episodes on the 3-day voiding diary, and 24-h pad weights. 4. Patient-reported outcome measures included I-QOL, SF-Qualiveen, NBSS, and PPBC.	10	1. No statistical difference was noted between both groups in terms of maximum cystometric capacity, the mean end of study bladder capacity was 369 in placebo group and was 305 mL for mirabegron group (p=0.20). 2. No statistical difference was noted between both groups in terms of all urodynamic parameters. 3. No statistically significant changes in functional bladder capacity (p=0.51), urinary frequency (p=0.55), and incontinence episodes (p=0.59) on the 3-day voiding diary, and 24-h pad weights (p=0.82). 4. There was statistically significant improvement in NBSS in favor of mirabegron group (p=0.04). 5. There was no statistically significant improvement in I-QOL (p=0.32), SF-Qualiveen (p=0.35), and PPBC (p=0.31).
Vasudeva et al. [35] (2021)	India/single center/RCT	Patients (>18 years) with a history of CVA with stable neurological status for at least past 3 months with symptoms of overactive bladder for ≥3 months	Mirabegron 50 mg	Darifenacin 15 mg	30/30	1. The primary outcome measures were urological efficacy (bladder diary parameters and the bladder sensation score) and neurological safety (MoCA-B scoring system). 2. The secondary outcome measures included non-neurological adverse effects (constipation, urinary retention, blurred vision, etc.).	12	1. There was a statistically significant improvement in bladder diary parameters and the bladder sensation score in each group, but without statistically significant differences on intergroup comparisons. In darifenacin group the mean frequency episodes/24 h. decreased from 11 to 7.5 after treatment (p<0.0001) and decreased from 11 to 8 after treatment in mirabegron group (p<0.0001), in intergroup comparison p=0.768, similarly mean frequency of Grade 3/4 bladder sensation/24 h decreased from 5.5 to 3 after treatment in darifenacin group (p<0.0001) and decreased from 5 to 3 after treatment in mirabegron group (p<0.0001), in intergroup comparison p=0.235, mean incontinence episodes/24 h decreased from 3 to 1 after treatment in both groups (p<0.0001 for each group) in intergroup comparison p=0.681. 2. There was no deterioration in the mean MoCA-B score in either of the groups after treatment, in both groups the score remain nearly similar, in darifenacin group p=0.448, and in mirabegron group p=0.489, intergroup comparison p=0.305. 3. The overall incidence of the adverse events was comparable between the two groups.

RCT, randomized controlled trial; OAB, overactive bladder; OABSS, OAB symptom score; IPSS, International Prostate Symptom Score; TSQ, treatment satisfaction questionnaires; PPBC, patient perception of bladder condition; GRA, global response assessment; MS, multiple sclerosis; LUTD, lower urinary tract dysfunction; MusiQoL, Multiple Sclerosis International Quality of Life questionnaire; NBSS, neurogenic bladder symptoms score questionnaire; PVR, post voiding residual volume; NDO, neurogenic detrusor overactivity; SCI, spinal cord injury; I-QOL, Incontinence Quality of Life questionnaire; VAS, visual analog scale; OAB-q SF, overactive bladder questionnaire short form; MCID, minimal clinical importance difference; SF-Qualiveen, short-form Qualiveen questionnaire; CVA, cerebrovascular accident; MoCA-B scoring system, Montreal Cognitive Assessment Basic.

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Table 2. Beta-3 adrenergic agonists compared to placebo for adults with neurogenic lower urinary tract dysfunction

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with β3 agonists
Urinary symptoms score - Assessed with: Overactive Bladder Symptom Score - Scale from: 0 to 15 (higher score indicating more severe symptom) - Follow-up: 12 weeks - MCID: 3[e]	192 (2 RCTs)	⊕⊕◯◯ Low[a,b,c]	-	The urinary symptoms score ranged from 7.74 to 10.5	MD 2.50 lower (4.78 lower to 0.22 lower)
Quality of life - Assessed with: Incontinence Quality of Life questionnaire - Scale from: 0–100 (higher score indicating less impact of lower urinary tract symptoms on quality of life) - Follow-up: 6 to 10 weeks - MCID: 4 points[f]	98 (2 RCTs)	⊕◯◯◯ Very low[a,d]	-	The quality of life ranged from 36.78 to 63.00	MD 10.86 higher (1.21 higher to 20.50 higher)
Major adverse events: cardiovascular side effects - Follow-up: 6 to 12 weeks - MCID: 3% absolute risk difference	310 (4 RCTs)	⊕⊕◯◯ Low[a,c]	RR 0.57 (0.14 to 2.37)	33 per 1,000	14 fewer per 1,000 (28 fewer to 45 more)
Overall adverse events - Follow-up: 6 to 12 weeks - MCID: 5% absolute risk difference	310 (4 RCTs)	⊕◯◯◯ Very low[a,d]	RR 0.88 (0.57 to 1.35)	219 per 1,000	26 fewer per 1,000 (94 fewer to 76 more)
Acute urinary retention - Follow-up: 6 to 12 weeks - MCID: 5% absolute risk difference	310 (4 studies)	⊕⊕⊕◯ Moderate[a]	RR 0.34 (0.01 to 8.15)	7 per 1,000	4 fewer per 1,000 (7 fewer to 47 more)

- Patient or population: adults with neurogenic lower urinary tract dysfunction.
- Setting: outpatient.
- Intervention: beta-3 adrenergic agonists.
- Comparison: placebo.

GRADE Working Group grades of evidence – High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; MCID, minimal clinically important difference; RCT, randomized controlled trial; MD, mean difference; RR, risk ratio.

[a]:Downgraded by one level for study limitations: unclear and/or high selection, performance, and detection bias.

[b]:Not downgraded further for inconsistency: despite substantial heterogeneity (I^2=92%) given that likely not clinically meaningful.

[c]:Downgraded by one level for imprecision: confidence interval crosses assumed threshold.

[d]:Downgraded by two levels for imprecision: wide confidence interval crosses assumed threshold and/or insufficient optimal information size.

[e]:Gotoh M, Homma Y, Yokoyama O, Nishizawa O. Responsiveness and minimal clinically important change in overactive bladder symptom score. Urology 2011;78:768-73.

[f]:Schurch B, Denys P, Kozma CM, Reese PR, Slaton T, Barron R. Reliability and validity of the Incontinence Quality of Life questionnaire in patients with neurogenic urinary incontinence. Arch Phys Med Rehabil 2007;88:646-52.

Table 3. Beta-3 adrenergic agonists compared to anticholinergics for adults with neurogenic lower urinary tract dysfunction

Outcome	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with anticholinergics	Risk difference with β3 agonists
Urinary symptoms score - Not reported.	-	-	-	-	-
Quality of life - Not reported.	-	-	-	-	-
Major adverse events: cardiovascular side effects - Cardiovascular side effects include: palpitation and hypertension - Follow-up: 12 weeks - MCID: 3% absolute risk difference	60 (1 RCT)	⊕◯◯◯ Very low[a,b]	Not estimable[c]	-	-
Overall adverse events - Follow-up: 12 weeks - MCID: 5% absolute risk difference	60 (1 RCT)	⊕◯◯◯ Very low[a,b]	RR 2.00 (0.19 to 20.90)	33 per 1,000	33 more per 1,000 (from 27 fewer to 663 more)
Acute urinary retention - Follow-up: 12 weeks - MCID: 5% absolute risk difference	60 (1 RCT)	⊕◯◯◯ Very low[a,b]	Not estimable[c]	-	-

- Patient or population: adults with neurogenic lower urinary tract dysfunction.
- Setting: outpatient.
- Intervention: beta-3 adrenergic agonists.
- Comparison: anticholinergics.

GRADE Working Group grades of evidence – High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI, confidence interval; MCID, minimal clinically important difference; RCT, randomized controlled trial; RR, risk ratio.

[a]:Downgraded by one level for study limitations: no information about allocation concealment, blinding, and selection of reported results.

[b]:Downgraded by two levels for imprecision: very rate event and insufficient optimal information size.

[c]:No events in both groups.

to 76 more) (Supplementary Fig. 4).

C. Acute urinary retention: Beta-3 adrenergic agonists probably result in little to no difference in acute urine retention (RR 0.34, 95% CI 0.01 to 8.15; 4 RCTs; 310 participants; moderate CoE) [30,32-34]. This would correspond to 4 fewer adverse events per 1,000 patients (95% CI 7 fewer to 47 more) (Supplementary Fig. 5).

D. Changes of voiding diary: There was no statistical difference in number of micturitions per day (MD -0.39, 95% CI -1.84 to 1.05; I^2=86%; 3 RCTs; 224 participants) [30,33,34], number of urgency episodes (MD -0.59, 95% CI -2.68 to 1.49; I^2=94%; 2 RCTs; 192 participants) [30,33] and number of incontinence episodes per day (MD -0.88, 95% CI -2.08 to 0.31; I^2=93%; 3 RCTs; 224 participants) [30,33,34] compared beta-3 adrenergic agonists to placebo (Supplementary Fig. 6).

(3) Subgroup and sensitivity analysis

We were unable to perform any predefined secondary analyses because there were no relevant data and no studies with a low risk of bias.

2) Beta-3 adrenergic agonists versus anticholinergics:

(1) Primary outcomes

No study reported urinary symptoms score and QOL outcomes. Based on 1 RCT with 60 patients (30 patients in each arm), no major adverse events (cardiovascular side effects) in either group occurred [35].

(2) Secondary outcomes

No study reported complications due to neurogenic disease. For overall adverse events. we are very uncertain about the effect of beta-3 adrenergic agonists (RR 2.00, 95% CI 0.19 to 20.90; 1 RCT; 60 participants; very low CoE) [35]. This would correspond to 33 more adverse events per 1,000 patients (95% CI 27 fewer to 663 more). Only 1 RCT with 60

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patients (30 patients in each arm) reported no acute urine retention events in either group [35]. There was no statistical difference in the number of micturitions per day (MD -0.09, 95% CI -0.93 to 0.74; I^2=0%; 2 RCTs; 151 participants) (Supplementary Fig. 7) [31,35], number of urgency episodes (MD -0.70, 95% CI -1.88 to 0.48; 1 RCTs; 60 participants) [31] and number of incontinence episodes per day (MD 0.00, 95% CI -0.78 to 0.78; 1 RCTs; 60 participants) [35] compared beta-3 adrenergic agonists to anticholinergics.

(3) Subgroup and sensitivity analysis

We were unable to perform any predefined secondary analyses because there were no relevant data and no studies with a low risk of bias.

4. Risk of bias

Overall, there is some concerns in bias arising from the randomization process due to the lack of a detailed explanation for allocation concealment in all of the six included studies. However, almost all studies have a high risk of bias in multiple domains such as bias arising from the randomization process and bias due to missing outcome data (Fig. 2). Therefore, all studies included in the analysis were rated as some concerns or a high risk of bias overall.

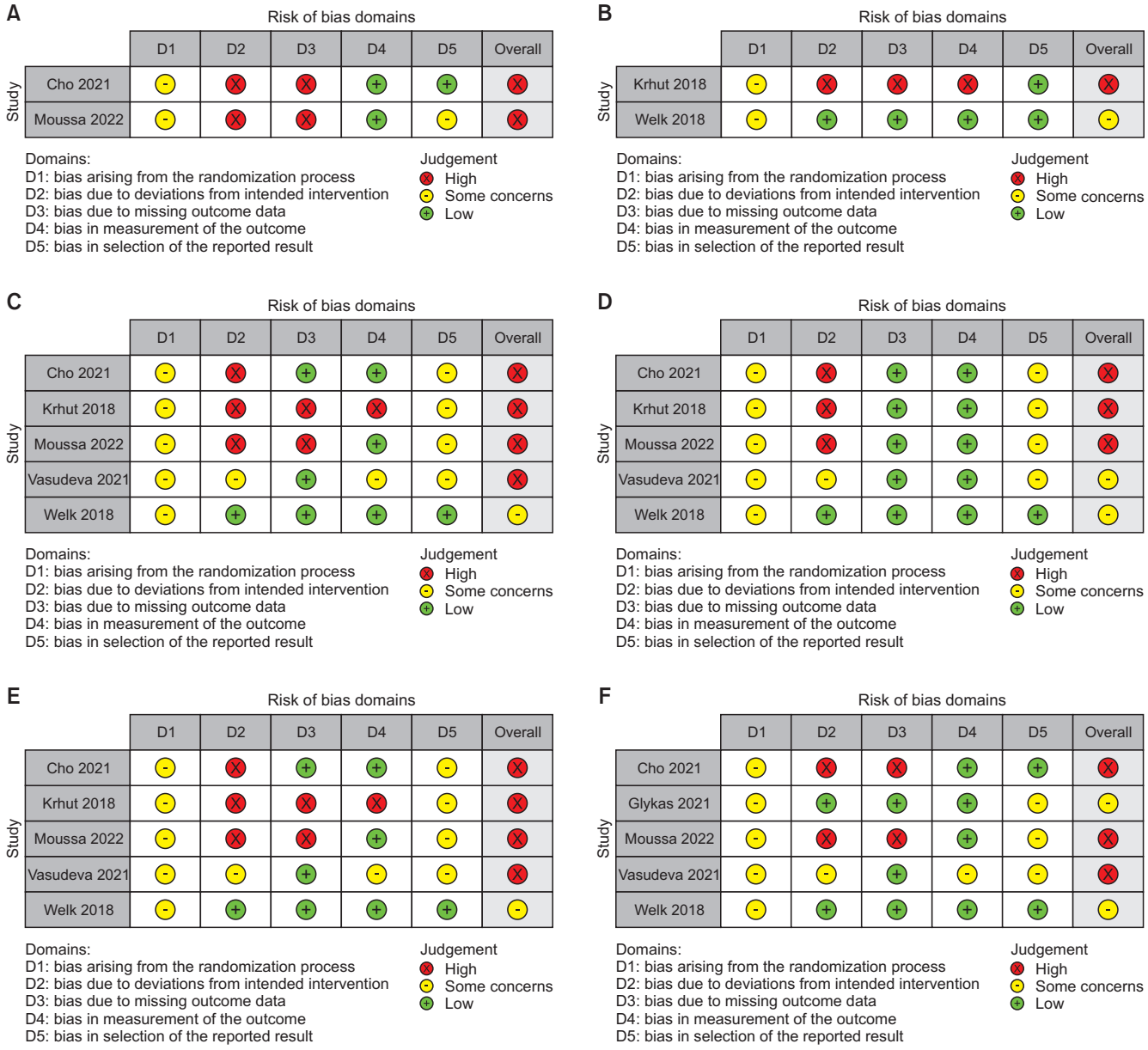

Fig. 2. Risk of bias (ROB) summary. (A) ROB for symptoms score improvement. (B) ROB for quality of life. (C) ROB for major adverse events (cardiovascular side effects). (D) ROB for overall adverse events. (E) ROB for acute urinary retention. (F) ROB voiding dairy. Figure created by robvis (https://www.riskofbias.info/welcome/robvis-visualization-tool).

5. Publication bias

Due to the small number of studies included in this review, funnel plots were not generated; therefore, publication bias may have been underestimated.

DISCUSSION

In light of available studies evaluating the use of beta-3 adrenergic agonists in NLUTD, we found six RCTs involving 461 adult patients with NLUTD due to multiple sclerosis, spinal cord injury, cerebrovascular accident, and parkinsonism with a follow-up period ranging from 6 to 12 weeks. Four compared mirabegron to a placebo, and the other two compared it to anticholinergics.

Comparing beta-3 adrenergic agonists to a placebo in NLUTD, beta-3 adrenergic agonists appear to have clinically unimportant effects on symptom improvement and similar effects on major adverse events rates. However, we are very uncertain about the effects of beta-3 adrenergic agonists on improving the QOL or overall adverse events rates. Although they probably result in little to no difference in the risk of acute urinary retention in patients with NLUTD compared to a placebo. Comparing beta-3 adrenergic agonists to anticholinergics, no study reported urinary symptom scores and QOL. In addition, we are very uncertain about the effects of beta-3 adrenergic agonists on major adverse events, overall adverse events, and acute urinary retention. In terms of voiding diary, there were no statistical differences in the number of micturitions, number of urgency episodes, and/or number of incontinence episodes per day when comparing beta-3 adrenergic agonists to placebo and anticholinergics.

Our review has limitations regarding the applicability of evidence. While we found six RCTs with NLUTD, most of them excluded patients with high post-void residual urine, indwelling Foley catheters, or intermittent catheterization.

Although a high percentage of patients with NLUTD had high post-void residual urine or were unable to self-void, they used a regular method of bladder emptying such as intermittent catheterization or indwelling Foley catheters. The very low incidence of acute urinary retention in our results is likely based on the strict inclusion criteria of the included RCTs.

There were also differences in the mean age of patients, different dosages of interventions, and comparators. In addition, none of the included studies reported the complications associated with neurogenic diseases, such as urinary tract infection, low bladder compliance, and renal insufficiency, despite their crucial significance not only for patients but also for physicians, especially concerning long-term patient follow-up. Also, the existing evidence was limited to relatively short-term outcomes up to 6 months' follow-up.

Moreover, some of the included studies focused primarily on urodynamic indicators, with fewer descriptions of symptoms, which made it challenging to comprehensively determine the efficacy of beta-3 adrenergic agonists [32,34]. Even in these studies, beta-3 adrenergic agonists did not improve urodynamic outcomes such as detrusor pressure or cystometric capacity, despite the significant improvement in urinary symptoms score [32,34].

While anticholinergics are a well-known first-line treatment for NLUTD, increasing bladder capacity and reducing urinary incontinence secondary to NLUTD [36], we found only two studies that compared beta-3 adrenergic agonists to anticholinergics with a very low level of evidence (CoE). One systematic review, evaluating the use of mirabegron in patients with NLUTD compared to anticholinergics, concluded that mirabegron may be an effective treatment in the management of neurogenic bladder unresponsive to antimuscarinics, particularly in patients presenting with storage symptoms. However, this review did not perform a meta-analysis due to the heterogeneity in the study PICOs [37].

Although combination therapy with drugs for voiding symptoms, such as alpha-blockers, has been recommended to maximize the efficacy of the treatment in patients with NLUTD [38], the included studies in our review only reported outcomes from mirabegron monotherapy.

Regarding previous meta-analyses for beta-3 adrenergic agonists in NLUTD, they have been sparse. A meta-analysis was published in 2021 which included only 4 RCTs largely focused on urodynamic parameters with less attention given to symptom assessment [39]. In 2022, another systematic review reported that mirabegron could improve urodynamic indicators and QOL with a low complication rate in patients with NLUTD. This systematic review included RCTs and non-randomized studies including prospective and retrospective cohorts [40]. Therefore, we advise caution with the interpretation of these findings, considering the inherent major risk of bias of non-randomized studies.

Apart from limitations regarding the applicability of evidence, methodological limitations should also be considered. First, a relatively small number of patients were included in the studies. Although the included studies were performed across the world (Asia, Europe, and North America), these studies were likely each conducted at single-center locations. Second, the review outcomes, which were reported in the included studies, were heterogeneous when combined in the analysis. Third, we found only low or very low CoE, signal-

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ing that our confidence in the reported effect size is limited or very limited, and this topic should be better informed by future research. Therefore, we need to be cautious when interpreting our meta-analysis for daily clinical practice.

However, our meta-analysis has several strengths. First of all, our review followed the rigorous methodology adopted by Cochrane Collaboration. We rated CoE according to the GRADE approach, which is a valuable guidance tool for decision making. Additionally, this review focused on patients' important outcomes such as urinary symptom scores, QOL, and major adverse events unlike previous systematic reviews that reported largely on urodynamic parameters with less emphasis on patient-important outcomes and none of them utilized the GRADE approach [37,39,40]. We also performed a comprehensive search using multiple databases, trial registries, and other grey literature sources without language restrictions.

In summary, there was a low or very low CoE on the effects of beta-3 adrenergic agonists on NLUTD compared to placebo and anticholinergics. It is hoped that more RCTs with higher methodological standards and long-term follow-up will be conducted in the future to strengthen the evidence about beta-3 adrenergic agonists. Additionally, research on drug combinations can be done to provide alternate options for NLUTD patients who do not respond well to monotherapy.

Finally, other molecules of beta-3 adrenergic agonists, such as solabegron, ritobegron, and vibegron, are currently being validated in clinical trials [41]. Therefore, their abilities to induce human detrusor relaxation should be elucidated for the treatment of NLUTD.

CONCLUSIONS

Compared to placebo, beta-3 adrenergic agonists may have similar effects on urinary symptom scores and major adverse events. There were uncertainties about their effects on QOL. Compared to anticholinergics, we are either very uncertain or have no evidence about urinary symptom scores, QOL, and major adverse events. The CoE for the outcomes of this review was low or very low, signaling that our confidence in the reported effect estimate is limited or very limited, and this topic should be better informed by future research.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Creating search strategies and searching for trials: Myung Ha Kim. Research conception and design: Mohamed Medhat Elkhashab, Abdullah Mari Alqahtani, and Jae Hung Jung. Data acquisition: Abdullah Mari Alqahtani, Jinu Kim, and Jang Hwan Kim. Statistical analysis: Mohamed Medhat Elkhashab, Abdullah Mari Alqahtani, Jinu Kim, Jang Hwan Kim, and Jae Hung Jung. Data analysis and interpretation: Mohamed Medhat Elkhashab, Abdullah Mari Alqahtani, and Jae Hung Jung. Drafting of the manuscript: Mohamed Medhat Elkhashab, Abdullah Mari Alqahtani, and Jae Hung Jung. Critical revision of the manuscript: Mohamed Medhat Elkhashab, Abdullah Mari Alqahtani, and Jae Hung Jung. Obtaining funding: Jinu Kim and Jang Hwan Kim. Administrative, technical, or material support: Jinu Kim. Supervision: Jae Hung Jung and Jang Hwan Kim. Approval of the final manuscript: Jae Hung Jung.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20230271.

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