

Efficacy of overactive neurogenic bladder treatment: A systematic review of randomized controlled trials

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Summary

Background: Overactive bladder (OAB) symptoms of frequency, urgency and urge incontinence are frequently associated with known neurological diseases like multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease (PD), stroke.

Objective: The aim of our study was to review the efficacy of pharmacological and non-pharmacological treatments for neurogenic overactive bladder.

Materials and methods: We searched two electronic databases (PubMed and EMBASE) for randomized controlled trials focusing on pharmacological and non-pharmacological medical treatments for overactive bladder symptoms associated with neurological diseases published up to 30 April 2022.

Results: A total of 157 articles were retrieved; 94 were selected by title and abstract screening; after removal of 17 duplicates, 77 records were evaluated by full-text examination. Sixty-two studies were finally selected. The articles selected for review focused on the following interventions: anticholinergics (n = 9), mirabegron (n = 5), comparison of different drugs (n = 3), cannabinoids (n = 2), intravesical instillations (n = 3), botulinum toxin (n = 16), transcutaneous tibial nerve stimulation (TTNS) (n = 6), acupuncture (n = 2), transcutaneous electrical nerve stimulation TENS (n = 4), pelvic floor muscle training (PFMT) (n = 10), others (n = 2).

Anticholinergics were more effective than placebo in decreasing the number of daily voids in patients with PD (mean difference [MD]- 1.16, 95 % CI - 1.80 to - 0.52, 2 trials, 86 patients, p < 0.004), but no significant difference from baseline was found for incontinence episodes and nocturia. Mirabegron was more

effective than placebo in increasing the cystometric capacity in patients with MS (mean difference [MD] 89.89 mL, 95 % CI 29.76 to 150.01, 2 trials, 98 patients, p < 0.003) but no significant difference was observed for symptom scores and bladder diary parameters. TTNS was more effective than its sham-control in decreasing the number of nocturia episodes (MD -1.40, 95 % CI -2.39 to -0.42, 2 trials, 53 patients, p < 0.005) but no significant changes of OAB symptom scores were reported. PFMT was more effective than conservative advice in decreasing the ICIQ symptom score (MD, -1.12, 95 % CI -2.13 to -0.11, 2 trials, 91 patients, p = 0.03), although the number of incontinence episodes was not significantly different between groups. **Conclusions:** The results of the meta-analysis demonstrate a moderate efficacy of all considered treatments without proving the superiority of one therapy over the others. Combination treatment using different pharmacological and non-pharmacological therapies could achieve the best clinical efficacy due to the favorable combination of the different mechanisms of action. This could be associated with fewer side effects due to drug dosage reduction. These data are only provisional and should be considered with caution, due to the few studies included in meta-analysis and to the small number of patients.

KEY WORDS: Overactive bladder; Urinary incontinence, Urge; Multiple sclerosis; Ischemic stroke; Parkinson disease; Anticholinergics; Mirabegron; Cannabinoids; Transcutaneous tibial nerve stimulation (TTNS); Pelvic floor muscle training (PFMT).

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INTRODUCTION

Voiding dysfunction often develops in patients with underlying neurological diseases. Patients may present with *overactive bladder* (OAB) symptoms of frequency, urgency and urge incontinence. OAB in patients with known neurological diseases (neurogenic overactive bladder) is related to disturbances of the neurological control of micturition. OAB symptoms are highly prevalent among patients with *multiple sclerosis* (MS), *spinal cord injury* (SCI), *Parkinson's disease* (PD), various neurological diseases, and stroke. This was shown by a recent study demonstrating OAB symptoms in over 50% of these patients (1). Symptoms vary from mild *lower urinary tract symptoms* (LUTS), that are often poorly recognized or misdiagnosed in men as prostatic disease, to severe clinical conditions like those observed after *spinal cord injury* (SCI). The severity of symptoms depends on the type and degree of damage to the nervous system. As the neurological condition progresses, the bladder function progressively deteriorates, and becomes more difficult to treat. Incontinence frequently develops as a consequence of disease progression.

Conservative management includes pharmacological treatment to reduce the contractility of the detrusor muscle, behavioral therapy and biofeedback, electrical stimulation, or chemical denervation procedures (instillation of capsaicin and resiniferatoxin or intradetrusorial injection of Botulinum toxin). No single treatment exists for neurogenic OAB due to the complexity and individual variability of the underlying neurological diseases. Treatment should be tailored to the individual patient, also considering that conventional treatment programs for non-neurogenic OAB could lack clinical efficacy in neurogenic patients.

Several systematic reviews have been published in the last 15 years to evaluate the evidence concerning the different treatments for neurogenic OAB (2-13).

In 2012, *Madhuvrata and coworkers* (2) published a systematic review and meta-analysis on anticholinergic treatment of adult neurogenic OAB, which updated and completed a previous systematic review assessing the efficacy and tolerability of anticholinergic agents in patients with OAB associated to multiple sclerosis (3). A more recent systematic review evaluated the effectiveness and safety of intravesical oxybutynin therapy for patients with neurogenic OAB (4). Two recent systematic reviews addressed the results of *pelvic floor muscle training* (PFMT) for bladder dysfunction in patients with multiple sclerosis (5, 6). One of these systematic reviews extended its analysis to the results of *peripheral tibial nerve stimulation* (PTNS) (6). A systematic review addressed the outcomes of PTNS in the treatment of lower urinary tract dysfunction including neurogenic bladder. PTNS was found to be effective in up to 100% of patients with neurological pathologies, although this review was based on non-randomized studies (7).

A meta-analysis evaluated the results of studies focusing on *sacral neuromodulation* (SNM) in patients with neurogenic lower urinary tract dysfunction (8).

Finally, several systematic reviews with metanalysis evaluated the treatment of overactive bladder syndrome with Botulinum toxin injection (9-15).

Although a relevant bulk of information from previous systematic reviews is available, certain specific aspects, such as

efficacy mirabegron and new anticholinergic agents in neurogenic bladder have not yet been addressed. Other issues, such as efficacy of PTNS in neurogenic bladder, need to be corroborated by randomized studies.

The aim of our study was to review the efficacy of treatments for neurogenic OAB focusing on recent clinical evidence, including studies focusing on mirabegron and on new anticholinergic agents.

MATERIALS AND METHODS

The review was conducted in accordance with the PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) guidelines (16). It has been registered on the PROSPERO platform (registration number: CRD42022347165).

Types of studies, inclusion criteria

We considered *randomized controlled trials* (RCTs), with single/double blinded design without time constraints.

We included studies involving adult patients of both sexes subjected to pharmacological and non-pharmacological medical treatment for overactive bladder symptoms associated with neurological diseases including post-ischemic stroke, Parkinson's disease and multiple sclerosis.

Outcomes

The following outcomes were considered: number of daytime voids and night-time voids (nocturia); number of incontinence and urgency episodes; modification of scores measuring urinary symptoms and quality of life; change of urodynamic measurements (cystometric capacity, peak pressure, volume at 1st contraction).

The *Overactive Bladder Symptom Score* (OAB-SS) is a diagnostic tool divided in four domains, administered to patients for self-evaluation of voiding symptoms. The score ranges between 0 and 15 (15 = most severe symptoms).

The *International Consultation on Incontinence Questionnaire Overactive Bladder* (ICIQ) is a questionnaire for evaluating overactive bladder and related impact on *quality of life* (QoL) and outcome of treatment in men and women in research and clinical practice across the world. It is based on a 0-16 overall score with greater values indicating increased symptom severity.

Search strategy

Two electronic databases (*PubMed* and *EMBASE*) were searched for articles in English, published up to 30 April 2022. Record search and retrieval was performed using strings based on the combination of various MeSH terms: (*Urinary Bladder, Overactive; Urinary Incontinence, Urge; Multiple Sclerosis; Ischemic Stroke; Parkinson Disease*): (treatment) AND (urge urinary incontinence OR overactive urinary bladder OR detrusor overactivity) AND (multiple sclerosis OR Parkinson disease OR ischemic stroke). Relevant data were also hand searched by browsing various sources (e.g., reference lists from reviews and study reports, congress abstracts, clinical trial registers such as www.clinicaltrials.gov, www.clinicaltrialsregister.eu, etc.).

Selection of studies

Retrieved papers were independently screened by two

authors by title and abstract to exclude documents that did not meet the inclusion criteria. Duplicate references were deleted. Full texts of selected papers were downloaded to confirm/reject inclusion and to extract relevant information. Controversies were resolved by a third researcher. A PRISMA flow diagram summarizes the study selection process (Figure 1).

Data extraction (Supplementary Materials PICO tables)

Data extraction was performed by four authors using a standardized form. The following information was obtained from each study: author(s), publication year, study design, population, interventions, comparisons, outcomes/end-points. In case of missing or insufficient information, we analyzed the reason for incompleteness and considered the impact of missing data on the meta-analysis results.

Quality evaluation (Supplementary Materials RoB evaluation)

Two authors independently performed the quality assessment by identifying potential biases using the 2019 Cochrane risk of bias tool (RoB) 2 (17). Study quality was assessed against pre-defined criteria in relation to randomization process (D1), deviations from the intended interventions (D2), missing outcome data (D3), measurement of the outcome (D4) and selection of the reported result (D5).

Disagreements were resolved by discussion.

The presence of high risk of bias was not used as a criterion to exclude studies from analysis.

Publication bias was planned to be assessed by funnel plot in the presence of at least 5 trials in each meta-analysis. If a potential reporting bias was found by visual inspection of the plots, the *Berg* and *Egger* tests were used to test funnel plots symmetry and to confirm the presence/absence publication bias.

A summary of findings table was generated, and the quality of the evidence emerging from meta-analyses including at least 3 studies was rated according to GRADE criteria.

Statistical analysis

Statistical analysis was performed using the RevMan5 software.

Mean differences, 95% confidence intervals (CI) and Z statistics were calculated (Random-effects model, inverse variance method).

Study heterogeneity was assessed by calculating the I^2 (and 95% CI), which was interpreted as of lesser importance ($I^2 \leq 40\%$), moderate ($I^2 = 30\%-60\%$), substantial ($I^2 =$

50%-90%) or considerable ($I^2 \geq 75\%$), according to Cochrane criteria. Sensitivity analysis was planned in case substantial or considerable heterogeneity of pooled analyses including at least 5 studies.

RESULTS

In total, 157 records (97 from Medline, 60 from EMBASE) were retrieved by database searching; 94 papers were included after title and abstract screening (62 from Medline, 32 from EMBASE).

After removal of 17 duplicates, we evaluated 77 papers by full-text reading. Twelve studies were excluded: five studies reported data contained in other included studies, a study evaluated the expression of CB1 and CB2 receptors after sublingual administration of spray cannabidiol, an article contained a review of the literature, two studies focused on non-neurogenic OAB, one study addressed a pediatric population, two studies were open-label.

Sixty-two studies were finally selected (Figure 1)

Table 1 lists the 62 studies included in this review, according to underlying disease and type of treatment.

Quantitative analysis was limited to the comparisons of mirabegron vs. placebo, anticholinergics vs. placebo, TTNS

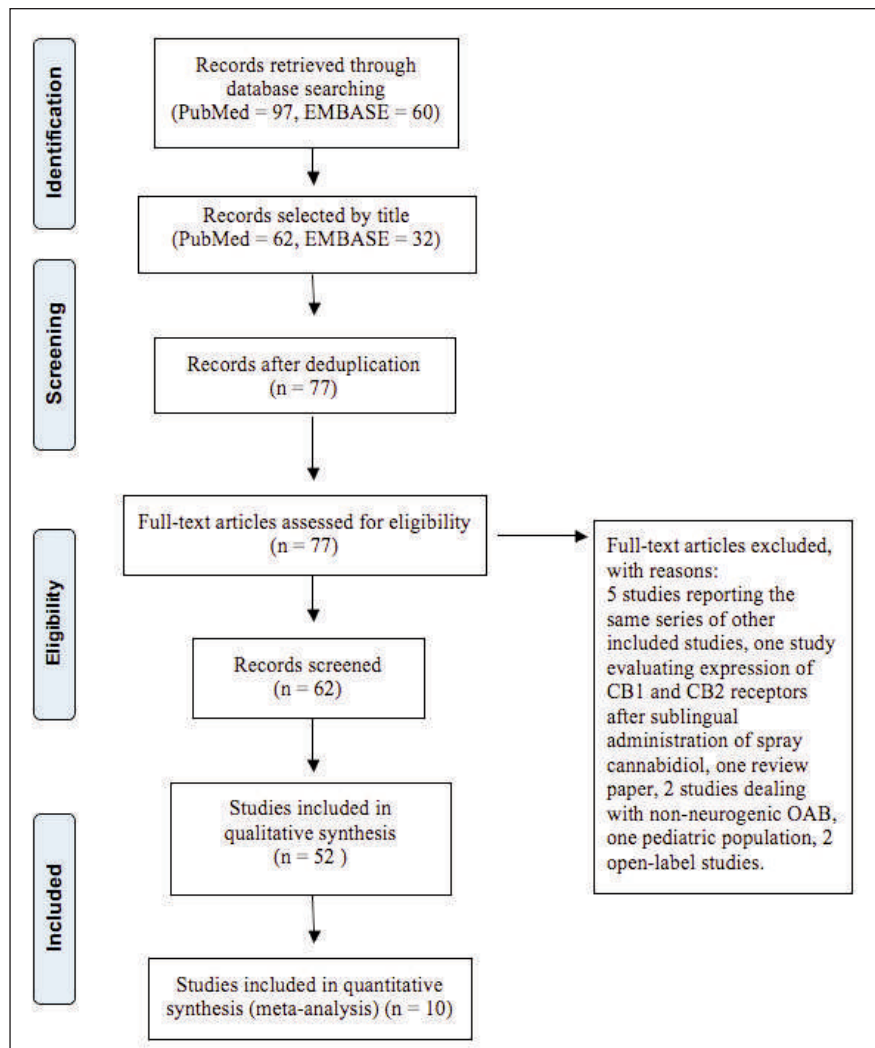


Figure 1.
Flow diagram.

Table 1.
Studies retrieved divided by treatment.

Treatment	Design	N° of studies	Disease
Mirabegron	Compared to placebo	5	PD (3), MS or SCI (2)
Anticholinergics	Compared to placebo	3	PD (2), MS or SCI (1)
	Compared to placebo to evaluate the cognitive effects of oxybutynin	1	Old people with cognitive impairment
	Oral trospium, standard vs. adjustable dose	1	Neurogenic detrusor overactivity
	Oral oxybutynin IR vs. intravesical oxybutynin or atropin	2	Neurogenic detrusor overactivity
	Propiverine IR vs. ER	1	Neurogenic detrusor overactivity
	Propiverine vs. Oxybutynin	1	Neurogenic detrusor overactivity
Comparison of drugs	Mirabegron vs. darifenacin	1	Poststroke
	Oxybutynin+trospium vs. oxybutynin+solifenacin	1	Neurogenic detrusor overactivity
	Milnacipran vs. paroxetine	1	Neurogenic detrusor overactivity
Cannabinoids	Compared to placebo	2	MS
Intravesical instillations	Capsaicin compared to saline	2	Spinal cord lesions Neurogenic detrusor overactivity
	Nociceptin/orphanin FQ	1	Neurogenic detrusor overactivity
Botulinum toxin	Compared to placebo	13	Neurogenic detrusor overactivity
	Trigone excluding vs. trigone including	2	
	Comparison of different doses	1	
Transcutaneous tibial nerve stimulation (TTNS)	Compared to sham	3	
	Compared to pelvic floor muscle training	1	
	Compared to oxybutynin	2	
Acupuncture		2	PD, poststroke
Transcutaneous electrical nerve stimulation (TENS)	Compared to sham	3	Poststroke (3)
	Compared to oxybutynin	1	
Pelvic floor muscle training (PFMT)	Compared to controls	6	PD (2), MS (2), poststroke (2)
	PFMT+electrostimulation vs. PFMT	3	MS (3)
	Compared to intravaginal neuromuscular electrical stimulation or to TTNS	1	
Others	Deep brain stimulation/ Intradetrusor adipose stem cells (ADSC) injections	2	PD

vs. sham intervention, and PFMT vs. controls. Other outcomes were not analyzed quantitatively because several extensive meta-analyses were previously published.

Anticholinergics

We found 9 papers evaluating the effects of anticholinergics (18-26).

Three papers compared anticholinergic agents with placebo for treatment of overactive bladder in patients with Parkinson disease (n = 2), multiple sclerosis or spinal cord injury (n = 1) (18-20).

Quantitative analysis of two studies (18, 19) in patients with Parkinson disease demonstrated that anticholinergics were more effective than placebo in decreasing the number of day voids (*mean difference* [MD], -1.16, 95% CI -1.80 to -0.52, 2 trials, 86 patients, Z = 3.56, p < 0.004). Changes from baseline number of incontinence and nocturia episodes were not significantly different between anticholinergics and placebo (MD, -0.44, 95% CI -1.23 to 0.35, 2 trials, 86 patients, Z = 1.08, P = 0.28, and MD, -0.36, 95% CI -1.17 to 0.45, 2 trials, 86 patients, Z = 0.87, p = 0.39, respectively) (Figure 2).

Adverse events associated with anticholinergics as dry mouth, constipation, and blurred vision are well known and may lead to therapy discontinuation.

In a study comparing solifenacin or oxybutynin with placebo the most common treatment emergent side effects were dry mouth and urinary tract infections although most events were considered mild in severity (20). Dry mouth was observed more frequently in patients taking oxybutynin (17%) than in those receiving solifenacin (4.2-7.8%) or placebo (2.3%). Changes from

baseline in VAS dry mouth score were significantly higher in the oxybutynin group than in placebo whereas there was no difference of VAS dry mouth score between solifenacin group and placebo. In another study, solifenacin was well tolerated but a case of urinary retention was observed in the treatment group (11%). Xerostomia and constipation were also observed (18).

During the treatment with fesoterodine 4 mg there was no serious adverse event and no urinary retention episode in both fesoterodine and placebo groups.

Xerostomia (3%) and constipation (3%) were observed in the treatment group (19).

One study demonstrated that short-term treatment using oral extended-release oxybutynin 5 mg once daily was safe and well tolerated compared to placebo (with no onset of delirium) in older female nursing home participants with mild to severe dementia (21).

Four studies compared the outcome of the treatment with anticholinergic agents administered at different dose, or as different formulations, or via different routes (22-25). Oral trospium chloride at standard dosage was compared with oral trospium chloride administered at adjustable doses. A therapeutic response was achieved in 58% of patients in the adjustable dose group and in 72% of those in the standard dose group (p = 0.23). Rates of side effects were similar between groups (35% vs 37%) (22).

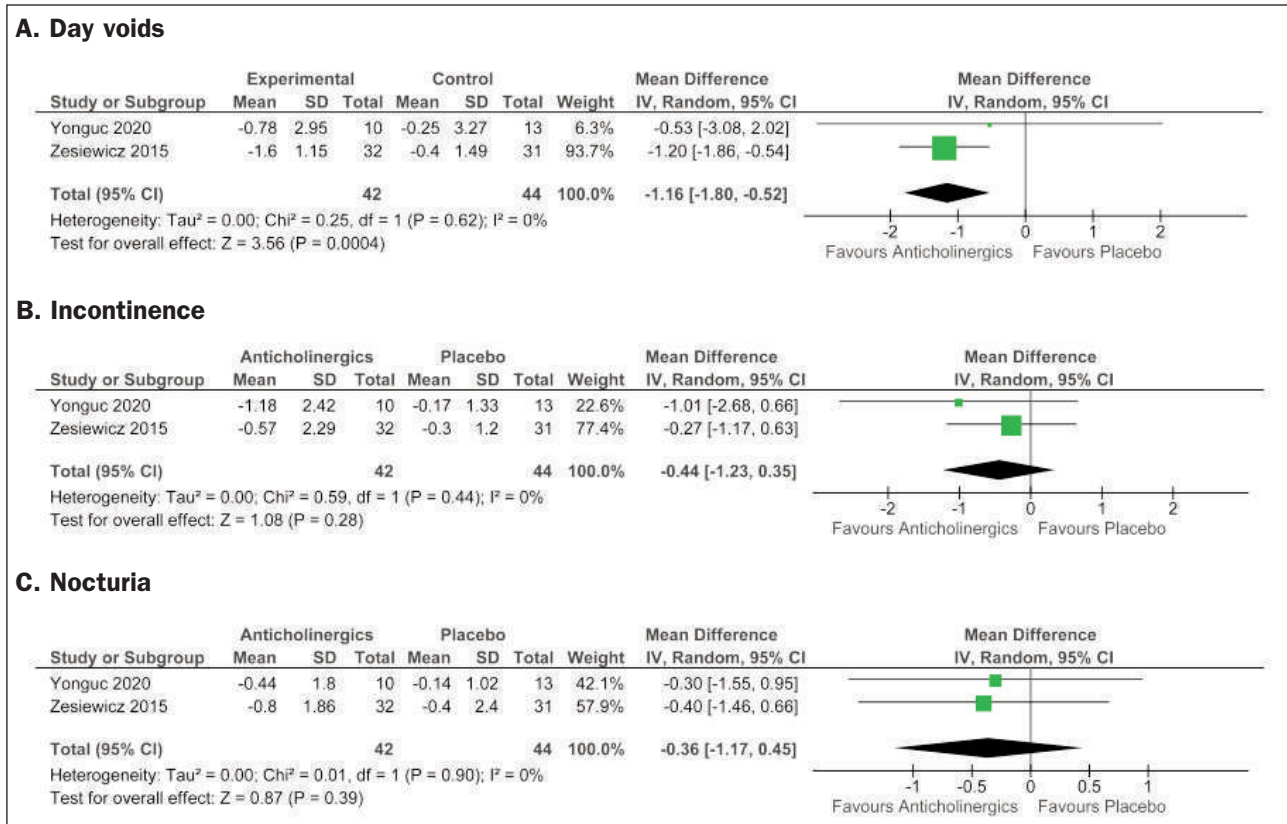
Oral treatment with oxybutynin immediate release was compared to intravesical oxybutynin or atropine.

The increase in maximum bladder capacity was higher with intravesical application, also causing less frequent and less severe side effects (23, 24).

Propiverine *extended-release* (ER) was compared with

Figure 2.

A, changes from baseline number of incontinence in patients with Parkinson disease treated with anticholinergics vs. placebo; B, changes from baseline number of night voids in patients with Parkinson disease treated with anticholinergics vs. placebo; C, changes from baseline number of day voids in patients with Parkinson disease treated with anticholinergics vs. placebo. Diamonds on the left side of the no-effect line indicate decreased numbers of episodes in patients treated with active drugs (anticholinergics) compared to placebo. Mean differences with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



propiverine immediate-release (IR). The latter showed slightly better tolerability compared to propiverine ER (25). The effects of propiverine and oxybutynin were compared in a study by Stöhrer *et al.* Both treatments increased maximum cystometric capacity and lowered maximum detrusor pressure during the filling phase with no significant differences between treatment groups. Adverse events were reported less frequently in the propiverine arm compared to the oxybutynin group (63.0% versus 77.8%) (26).

Mirabegron

We retrieved five RCTs comparing mirabegron vs. placebo in patients with OAB and Parkinson disease ($n = 3$) (27-29) or spinal cord injury/multiple sclerosis ($n = 2$) (30, 31).

Three studies evaluated the clinical results of mirabegron treatment in patients with Parkinson disease. Changes from baseline values of the OAB-SS score, day void rates or of incontinence and urgency episodes were not significantly different between mirabegron and placebo (MD, -2.01, 95% CI -4.24 to 0.21, 2 trials, 212 patients, $Z = 1.78$, $p = 0.08$; MD, -0.80, 95% CI, -3.04 to 1.43, 2 trials, 227 patients, $Z = 0.71$, $p = 0.48$; MD, -0.11, 95% CI -3.12 to 2.91, 2 trials, 195 patients, $Z = 0.07$, $p = 0.94$; MD, -0.56, 95% CI -1.88 to 0.75, 3 trials, 227 patients, $Z = 0.84$, $p = 0.40$; respectively) (Figure 3, panels A, B, C and D).

Two studies evaluated changes of urodynamic values in patients with spinal cord injury/multiple sclerosis treated with mirabegron. Mirabegron was more effective than placebo in increasing cystometric capacity (MD, 89.89 mL, 95% CI 29.76 to 150.01, 2 trials, 98 patients, $Z = 2.93$, $p < 0.003$). Changes from baseline values of peak pressure and volume at first contraction were not significantly different between mirabegron and placebo (MD, -13.34 cm², 95% CI -55.70 to 29.01, 2 trials, 97 patients, $Z = 0.62$, $P = 0.54$ and MD, 22.92 mL, 95% CI -20.78 to 66.63, 2 trials, 98 patients, $Z = 1.03$, $p = 0.30$, respectively) (Figure 4 A, B and C).

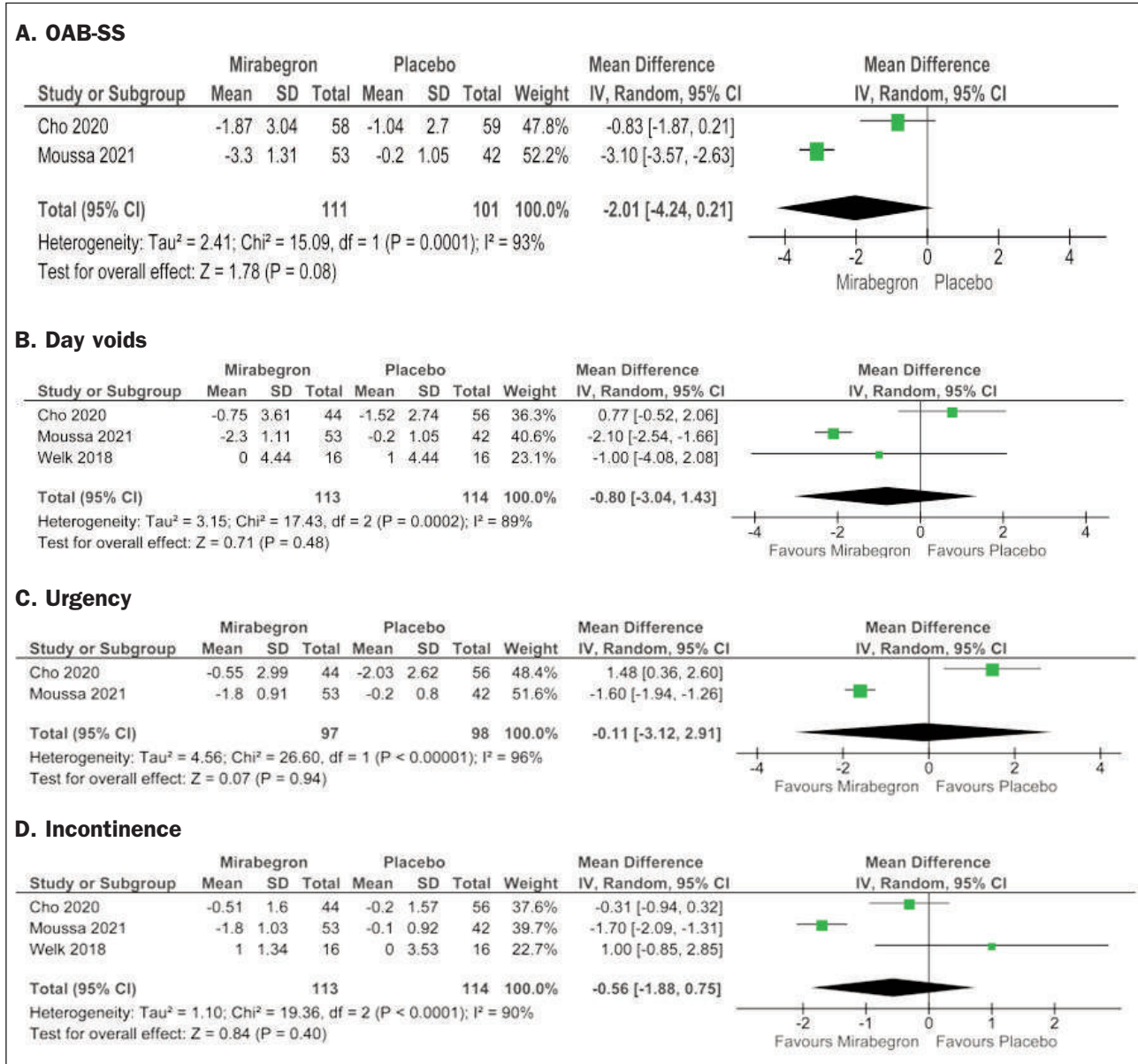
In general, the rate of treatment emergent adverse events was similar in the mirabegron and placebo groups and the degree of adverse events was mild or moderate in most cases.

A major safety concern with mirabegron is cardiovascular safety because of beta-adrenergic stimulation. In three studies changes in cardiovascular parameters were actively assessed demonstrating no significant changes of mean systolic and diastolic blood pressure, pulse rate, and QTc interval during mirabegron treatment (28, 30, 31).

The risk of urinary retention is another concern associated to mirabegron treatment. Data from two studies (27, 31) showed no significant change of mean post-voiding residual volume or proportion with PVR > 100 ml,

Figure 3.

A, changes from baseline values of OAB-SS scores after mirabegron vs. placebo in patients with Parkinson disease;
 B, changes from baseline number of day voids after mirabegron vs. placebo in patients with Parkinson disease;
 C, changes from baseline number of urgency episodes after mirabegron vs. placebo in patients with Parkinson disease;
 D, changes from baseline number of incontinence episodes after mirabegron vs. placebo in patients with Parkinson disease.
 Diamonds on the left side of the no-effect line indicate decreased numbers of episodes or symptom scores in patients treated with mirabegron compared to placebo. Mean differences with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



whereas in a study a case with PVR > 100 was described in mirabegron group but not in placebo (28).

Comparison between various drugs

Three studies compared the efficacy and safety of different drugs used for treatment of neurogenic OAB.

In patients who had ischemic stroke, mirabegron and darifenacin showed similar improvement of bladder diary parameter without deterioration of cognitive function (32).

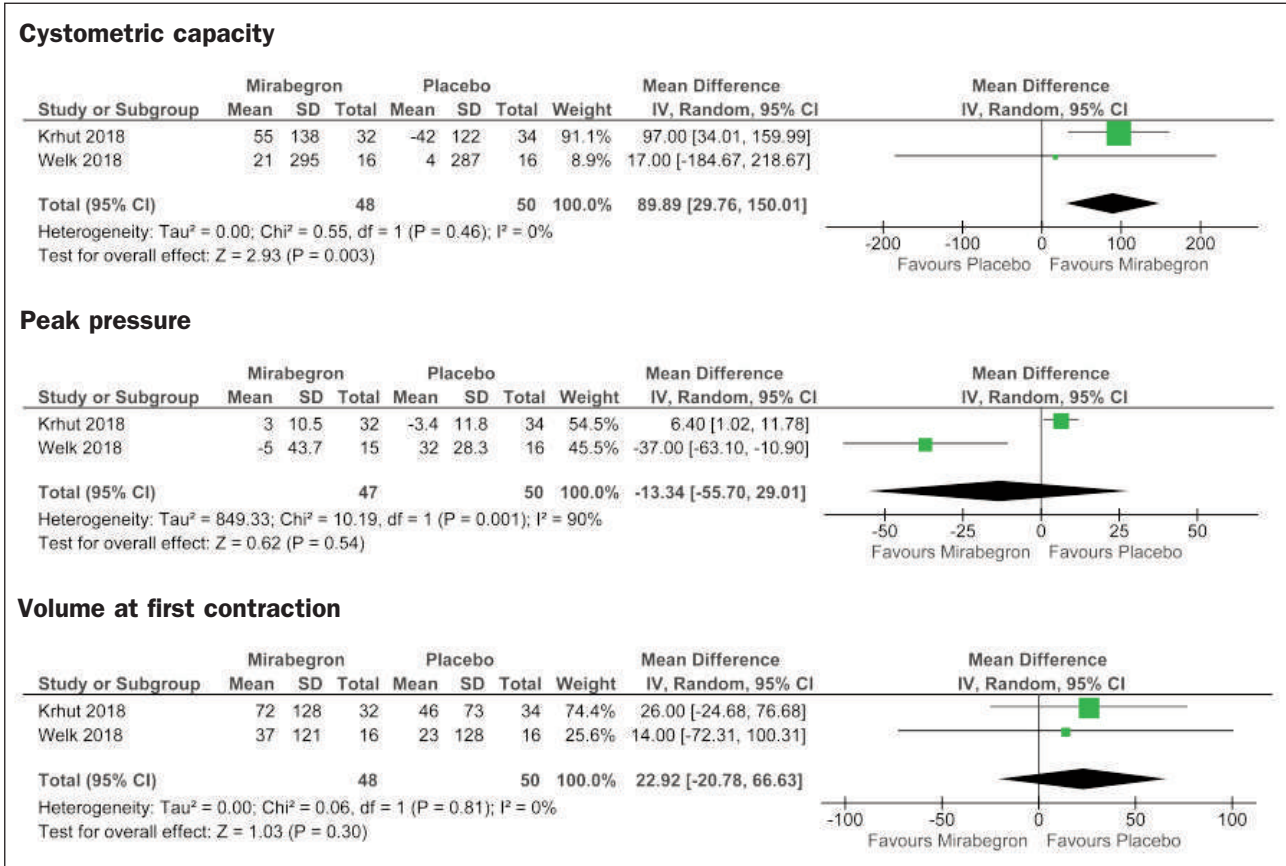
Both combination of trospium chloride with oxybutynin, and solifenacin with oxybutynin improved subjective

and urodynamic urinary parameters, though side effects were higher in patients taking oxybutynin plus solifenacin (33).

A study proposed the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) as an alternative to anticholinergic treatment in order to minimize antimuscarinic or cardio-suppressive effects. SNRIs are currently used for treatment of depression, though the SNRI duloxetine has been used to treat stress urinary incontinence thanks to its activity on the urinary sphincter, presumably via serotonergic and adrenergic receptors of the sacral *Onuf's* nucleus. SNRIs lack anticholinergic properties, unlike conventional

Figure 4.

A, changes of cystometric capacity values in patients with spinal cord injury/multiple sclerosis treated with mirabegron vs. placebo; B, changes of peak pressure values in patients with spinal cord injury/multiple sclerosis treated with mirabegron vs. placebo; C, changes of volume at 1st contraction values in patients with spinal cord injury/multiple sclerosis treated with mirabegron vs. placebo. Diamonds on the right side of the no-effect line indicate increased cystometric capacity (A) and volume at first contraction (C) in patients treated with mirabegron compared to placebo. Diamonds on the right side of the no-effect line indicate decreased peak pressure in patients treated with mirabegron compared with placebo. Mean differences with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



antidepressants, and stimulation of serotonergic receptors seems to suppress bladder contractility. For this reason, SNRIs could have a role in the treatment of neurogenic OAB. A study compared the effect of the SNRI milnacipran on OAB symptoms compared to paroxetine, a selective serotonin reuptake inhibitor (SSRI) lacking adrenergic effect. Milnacipran, but not paroxetine, improved the quality of life of patients by reducing daytime urinary frequency and by increasing the bladder capacity (34).

Cannabinoids

Two studies reported the effect of cannabis-containing medicines in patients with overactive bladder and multiple sclerosis (35, 36).

Cannabinoids (cannabis extract, Δ9-tetrahydrocannabinol or THC, nabiximols or Sativex) were used to treat OAB in patients with MS. Cannabis extract and THC reduced incontinence episode rates by 38% and 33%, respectively. Sativex, an endocannabinoid system modulator, significantly reduced nocturia episodes and daytime voids. Dizziness (16%), disorientation (6%) and dissociation (6%) were observed during treatment.

Intravesical instillations

In two studies, a single intravesical instillation of capsaicin significantly decreased voiding frequency and incontinence episodes, increased the maximum cystometric capacity and decreased the maximum detrusor pressure (37, 38). Capsaicin diluted in ethanol solvent caused significant side effects in 70% of cases, whereas side effects were limited using a glucidic solvent. The therapeutic effect of capsaicin is time-limited with no significant efficacy observed after three months. Intravesical instillations of nociceptin/orphanin FQ also decreased urine leakages and increased the voiding bladder capacity without significant side effects (39).

Botulinum toxin

Thirteen studies evaluated the effect of Botulinum toxin intra-detrusor injection compared to saline injection in patients with neurogenic detrusor overactivity associated with spinal injury or multiple sclerosis (40-52). Intravesical Botulinum toxin treatment proved to be effective and safe for the treatment of neurogenic detrusor overactivity. Transient adverse events were urinary retention,

hematuria, muscle weakness, and urinary tract infection. Two studies compared the effect of injections in the detrusor excluding the trigone with injections including the trigone (53, 54).

A study compared the effect of the administration of two different doses of Botulinum toxin type A (55).

Most of these studies were included in recently published meta-analyses.

Our search added to published systematic reviews three studies which were published after 2017. *Kennelly et al.* reported pooled data from two phase 3 studies assessing the safety and efficacy of abobotulinumtoxinA (aboBoNT-A) in patients with neurogenic detrusor overactivity who were routinely performing clean intermittent catheterization. Treatment with aboBoNT-A significantly reduced incontinence episodes per week in comparison to placebo ($p < 0.001$) and significantly increased the volume per void *Denys et al.* compared the administration of abobotulinumtoxinA by 15 intra-detrusor injections in comparison to 30 injections (43).

Both 15 and 30 injections administration modes decreased the daily number of incontinence episodes and improved urodynamic parameters in patients with NDO.

Honda et al. described the results of the administration of onabotulinumtoxinA in Japanese patients with neurogenic detrusor overactivity, demonstrating reduction of urinary incontinence episodes and improvement of urodynamic parameters (47).

Transcutaneous tibial nerve stimulation (TTNS)

Six studies reported the results of TTNS in neurogenic OAB. Three studies compared active treatment with sham treatment (56-58) and 3 compared TTNS with other treatments such as pelvic floor muscle training (59) or oral anticholinergics ($n = 2$) (60, 61).

TTNS reduced urinary frequency, urgency, and incontinence episodes in comparison to placebo.

Quantitative analysis of two studies comparing TTNS with sham treatment in patients with Parkinson disease shows that TTNS was more effective than sham in decreasing the number of nocturia episodes (MD, -1.40, 95% CI -2.39 to -0.42, 2 trials, 53 patients, $Z = 2.79$, $p < 0.005$). Changes from baseline of OAB scores were not significantly different between TTNS and sham (MD -2.87, 95% CI -17.25 to 11.51, 2 trials, 53 patients, $Z = 0.39$, $p = 0.70$) (Figure 5A, B).

In a study including patients with multiple sclerosis, quality of life scores (SF-Qualiveen), overactive bladder symptom scores (USP) and rates of urgency episodes were improved after both PFMT and TTNS but no differences between the two groups were observed (59).

TTNS was compared to oxybutynin (5 mg BID) in patients with OAB and multiple sclerosis. TTNS showed a less significant reduction of OAB-S (overactive bladder symptoms) and OAB-Q (overactive bladder quality of life) scores in comparison to oxybutynin, though the latter was associated with a higher rate of side effects (35%) (60).

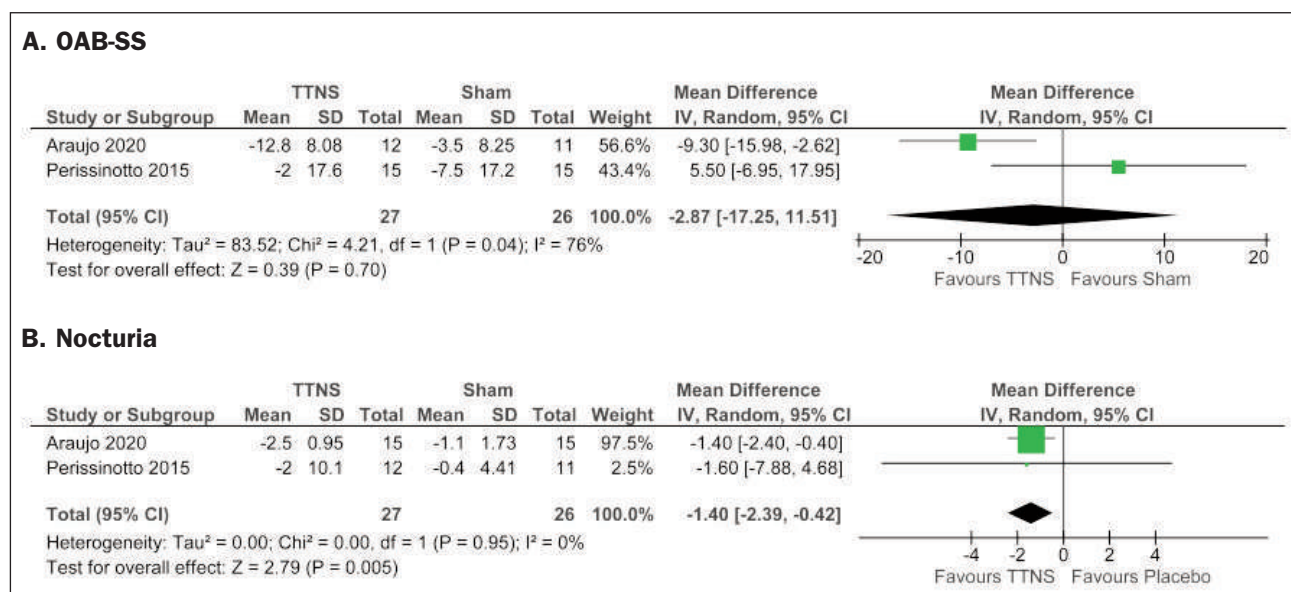
In another study including women with neurogenic bladder, the association of TTNS with tolterodine 4 mg improved urgency symptoms (61).

Acupuncture

The effect of acupuncture and electroacupuncture was reported in 2 studies in patients with Parkinson's disease and post-stroke OAB. In PD patients, acupuncture associated with a low dose of tolterodine (1 mg BID) improved daily rates of frequency and incontinence as well as mean urine volumes more than full-dose tolterodine (2 mg BID) (62). In post-stroke patients, electroacupuncture treatment improved the perceived severity of OAB symptoms in com-

Figure 5.

A, changes from baseline of OAB scores in patients with Parkinson disease treated with TTNS vs sham treatment; B, changes from baseline of the number of night voids in patients with Parkinson disease treated with TTNS vs sham treatment. Diamonds on the left side of the no-effect line indicate decreased numbers of episodes or symptom scores in patients treated with TTNS compared to sham treatment. Mean differences with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



parison with standard care, though no significant differences were observed in bladder diary parameters and *quality of life scores* (SSQoL). Both acupuncture and electroacupuncture were well tolerated (63).

Transcutaneous electrical nerve stimulation (TENS)

Transcutaneous electrical nerve stimulation has been used to treat post-stroke neurogenic overactive bladder. Positive pads were usually placed in the region of the second sacral level of the vertebral column and negative pads were placed at the level of the middle and lower third of the junction between the posterior superior iliac spine and the ischial node. Treatments were administered 30 minutes once a day for 60-90 days, in the form of unidirectional square waves with different combinations of pulse duration and frequency.

In three studies, TENS was compared to sham treatment for treatment of post-ischemic stroke urinary incontinence, whereas one study compared TENS to anticholinergic drugs (64-67).

TENS improved symptom scores, voiding diary parameters (daily micturition, nocturia, urgent urination, and urge UI), and urodynamic findings (maximum cystometry volume, flow rate, pressure of detrusor in the end of the filling phase).

In the study comparing TENS with anticholinergics, the former was superior than the latter.

Pelvic floor muscle training

Six studies evaluated the outcome of behavioral therapy, including *pelvic floor muscle training* (PFMT) in comparison with controls (2 in Parkinson disease, 2 in incontinence post-stroke, 2 in multiple sclerosis) (68-73).

The quantitative analysis of the results of two studies in patients with Parkinson disease comparing pelvic floor muscle training with conservative advice, demonstrated that PFMT was more effective than the latter in decreasing the values of the ICIQ score (MD -1.12, 95% CI -2.13 to -0.11, 2 trials, 91 patients, Z = 2.17, p = 0.03). The number of incontinence episodes from baseline was not significantly different between PFMT and controls (MD, -0.41, 95% CI -2.84 to 2.03, 2 trials, 91 patients, Z = 0.33, p = 0.74) (Figure 6). Other studies compared PFMT plus vaginal electrostimulation to home PFMT in patients with multiple sclerosis (74-77).

In patients with multiple sclerosis and LUTS, the association of PFMT (with EMG feedback) and intravaginal NMES significantly improved pelvic floor muscle assessment findings and OAB-V8 scores more than PFMT alone and the association of PFMT with TTNS.

Three studies from the same group compared outcomes of PFMT alone with PFMT with vaginal electrostimulation in women with LUTS in multiple sclerosis. OAB-V8 scores, quality of life and perineal musculature contraction were improved after both treatments, although a greater increase was obtained with the addition of electrostimulation.

Other studies

Deep brain stimulation (DBS), a surgical treatment for motor symptoms in advanced PD, showed improvement of LUTS in PD patients (78).

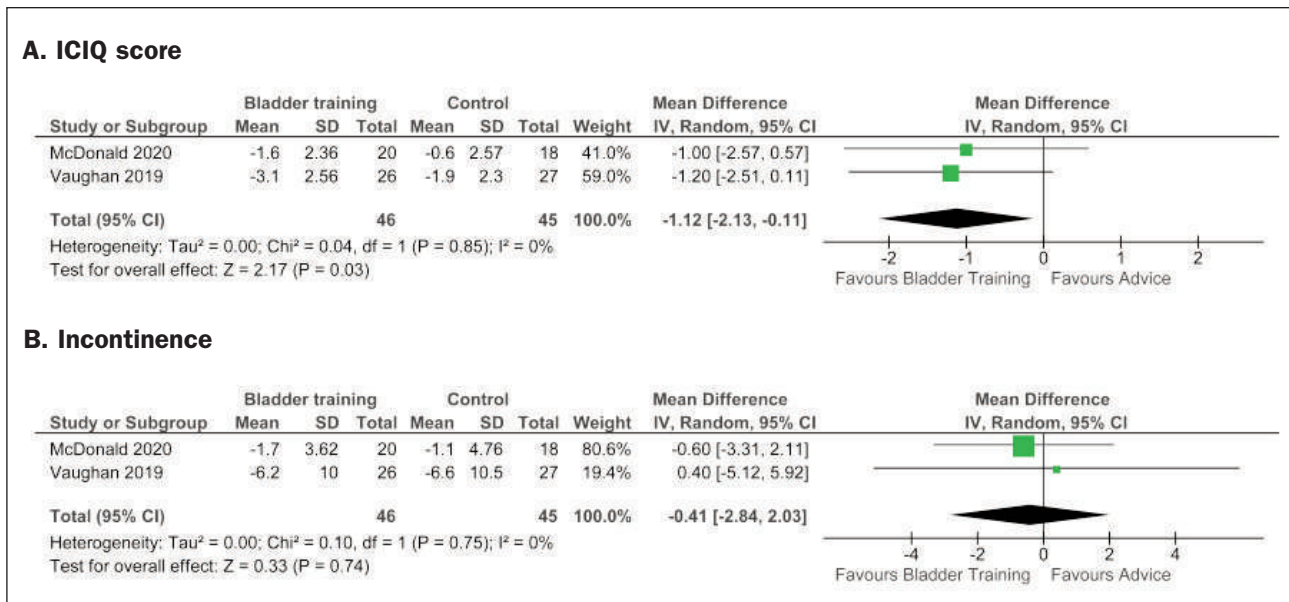
Intra-detrusor injections of *adipose stem cells* (ADSC) were also used to treat PD-related OAB symptoms. A single ADSC injection significantly improved symptom scores and voiding diary parameters (79).

Figure 6.

A, changes from baseline of ICIQ-OAB scores in patients with Parkinson disease treated with pelvic floor muscle training vs. conservative advice;

B, changes from baseline of the incontinence episodes in patients with Parkinson disease subjected to the same treatments.

Diamonds on the left side of the no-effect line indicate decreased numbers of episodes or symptom scores in patients treated with PFMT compared to advice. Mean differences with 95% confidence intervals and heterogeneity statistics (I^2) are shown.



DISCUSSION

Anticholinergics

Anticholinergics are the first-line choice for the pharmacologic treatment of OAB. They are used to stabilize the detrusor muscle and improve bladder compliance because detrusor smooth contraction is initiated via release of acetylcholine. The major disadvantage of oral anticholinergics are the side effects that result in treatment discontinuation in up to 70% of patients, depending on the duration of treatment. Furthermore, a potential risk of cognitive decline and worsening of gait in patients with PD has been recently suggested.

In 2009, a Cochrane systematic review assessed the efficacy and tolerability of anticholinergic agents in patients with overactive bladder associated to *multiple sclerosis* (MS) (3). Only three RCTs were considered suitable for analysis. An older randomized cross-over study compared methantheline bromide, flavoxate chloride and meladrazine tartrate (*Hebjorn 1977*) (81). A more recent study found reduced symptoms after oxybutynin compared to propantheline (*Gajewski 1986*) (82). Finally, a study found no significant difference in term of efficacy between oral oxybutynin and intravesical atropine, although side effects and quality of life were in favor of the latter (*Fader 2007*) (83). The Authors concluded that evidence was insufficient to demonstrate any benefit from the administration of anticholinergics for urinary symptoms in multiple sclerosis. In addition, high rates of adverse effects were reported, with 20% of patients who had to withdraw from oral treatment.

In a systematic review by *Madhuvrata et al.* (2), eight RCTs comparing anticholinergic drugs with placebo in adult neurogenic OAB were included. The meta-analysis of three studies showed higher maximum cystometric capacity, higher volume at first contraction, and lower maximum detrusor pressure after anticholinergics compared to placebo. On the contrary, no significant changes in frequency of micturition or incontinence episodes per 24 hours were observed.

The present review included three RCTs (18-20) comparing anticholinergics with placebo, which were published after the review of *Madhuvrata et al.* In patients with Parkinson disease, anticholinergics were more effective than placebo in decreasing the number of day voids, though the number of incontinence episodes and nocturia were not significantly decreased.

The most frequent side effect was dry mouth which was observed in 17% of the patients taking oxybutynin.

Similarly, the meta-analysis of *Madhuvrata et al.* (2) showed statistically significantly higher dry mouth with anticholinergic drugs compared with placebo (32 vs 7%), but did not report any statistically significant difference in any other adverse event, nor in withdrawal rates due to adverse events (8 vs 2%). There were no statistically significant differences in any of the outcomes between oxybutynin and other anticholinergics nor among different doses and preparations of anticholinergic drugs.

A meta-analysis of RCTs on the efficacy and safety of anticholinergic drugs for non-neurogenic overactive bladder (83) concluded that extended-release formulations showed some advantages when compared to immediate

release ones, both in terms of efficacy and safety. No significant advantage was observed after transdermal delivery compared to oral intake.

In general, dose escalation obtained some improvements in term of efficacy, although it was associated with a significant increase in the rate of adverse events. Tolterodine IR was associated with less adverse events than oxybutynin IR.

In our review, we included three studies comparing the effect of the treatment with anticholinergic agents administered at different doses or with different formulation.

Oral trospium chloride at standard doses and at adjustable doses showed similar therapeutic responses and similar rates of side effects (22). Similarly, when compared to propiverine IR, propiverine ER showed a slightly better tolerability (25).

A comparison of propiverine vs. oxybutynin showed no significant differences in the increase of maximum cystometric capacity and decrease of maximum detrusor pressure during the filling phase. Adverse events were reported less frequently in the propiverine arm compared to the oxybutynin group (63.0% versus 77.8%) (26).

Shen et al. (4) recently reviewed randomized and non-randomized studies evaluating effectiveness and safety of intravesical oxybutynin therapy for patients with neurogenic detrusor overactivity compared to oral oxybutynin. In studies in adults, maximum bladder capacity increased and detrusor pressure at maximum bladder decreased more after intravesical oxybutynin than after oral treatment. After treatment, 76.9% of adult patients were considered “dry or improved”. Side effects were reported in 13.5% of cases and 6.6% of patients withdraw for side effects.

Our review did not add any new study on intravesical anticholinergic administration to *Shen's* meta-analysis.

Combined administration of two different anticholinergic drugs instead of standard of care (a single antimuscarinic drug administered at maximum of recommended dosage) was proposed to improve efficacy without affecting tolerability. Combined administration of trospium chloride with oxybutynin and solifenacin with oxybutynin (33) improved subjective and urodynamic urinary parameters, although side effects were higher in patients taking oxybutynin plus solifenacin.

Mirabegron

Mirabegron is a beta-3 adrenoceptor agonist that mediates bladder relaxation and facilitates the filling phase by stimulating beta-3 adrenoceptors. Mirabegron is commonly used for idiopathic OAB treatment because of its efficacy, comparable to that of anticholinergic drugs, but with a better tolerability profile (84, 85). However, mirabegron may affect the cardiovascular system causing hypertension, increased heart rate, arrhythmias, and headache (86). Patients with neurogenic OAB could be more exposed to such side effects because of potential disturbances of the vegetative nervous system. In particular, this could be the case in patients with SCI above the T6 level that is above the outflow of splanchnic sympathetic fibres. Our meta-analysis partially supported the efficacy of mirabegron in patients with neurogenic overactive bladder. The cystometric capacity was increased after

mirabegron in patients with MS, although peak pressures and volume at 1st contraction were not significantly increased. Symptom scores and bladder diary parameters were not significantly changed in patients with PD.

Cardiovascular parameters were not significantly affected by mirabegron treatment although patients at risk for cardiovascular disease were excluded from most trials.

Mirabegron was compared to darifenacin in the treatment of OAB in patients with a history of cerebrovascular accident (32). No differences in bladder diary parameters were observed between groups. No patients developed intolerable severe adverse effects and no deterioration in the cognitive function assessed using MoCA-B scores was observed in either arm.

Cannabis-containing medicines

Cannabis-containing medicines were used in the treatment of OAB in patients with multiple sclerosis. The potential mechanism of action of those medicines is not fully elucidated, although it could be mediated by CB1 receptors or by *transient receptor potential vanilloid 1* (TRPV1) receptor in the bladder. In our review, two RCTs were included, showing that treatment with THC or *cannabidiol* (CBD) reduced episodes of incontinence, daytime voids and nocturia.

Other oral treatments

A possible alternative to anticholinergics is milnacipran, a serotonin and noradrenaline reuptake inhibitor (SNRI) which can suppress bladder contractility by stimulating serotonergic receptors. In a single study, this drug was able to reduce daytime urinary frequency and to increase bladder capacity (34).

Intravesical instillations

Prevention of micturition reflex to trigger bladder overactivity represents a possible alternative to drugs blocking smooth muscle contraction like anticholinergics. Drugs like capsaicin, RTX, and nociception/orphanin FQ have an effect on the unmyelinated C-fiber afferent limb of the micturition reflex.

Instillations of both capsaicin and nociceptin/orphanin FQ were able to decrease incontinence rates and to improve urodynamic parameters in patients with neurogenic OBA (37-39).

Botulinum toxin injections

Botulinum toxin has been used for many years in the treatment of severe neurogenic overactive bladder refractory to standard treatment. In 2007, *Duthie et al.* published a systematic review on the treatment of overactive bladder syndrome with botulinum toxin injections. The review, which was updated in 2011 (9), included patients affected by either neurogenic OAB or idiopathic OAB. Botulinum toxin injection was superior to placebo in all studies included in the analysis, with an effect lasting for several months depending on the dose and the type of toxin used. Other systematic reviews with meta-analysis were subsequently published to confirm the efficacy and safety of this treatment.

Zhang et al. (10) retrieved eight RCTs focusing on efficacy and safety of onabotulinumtoxinA in patients with

neurogenic detrusor overactivity (NDO), published up to September 2012. Infiltrations with onabotulinumtoxinA improved maximum cystometric capacity and decreased maximum detrusor pressure compared to placebo. The treatment was more frequently associated with UTIs than placebo. No dose-related differences of efficacy and side effects were observed when regimens based on 300 U or 200 U doses were compared.

Similarly, *Zhou et al.* (11) searched databases (up to November 2013) to identify RCTs focusing on the effect of onabotulinumtoxinA for treatment of NDO.

The authors included four studies in their analysis, which confirmed a dose-independent reduction of the number of urinary incontinence episodes per week, the increase of maximum cystometric capacity, and the reduction of maximum detrusor pressure compared to placebo. OnabotulinumtoxinA was more often associated with the onset of UTIs, hematuria and urinary retention.

Mehta et al. (12) retrieved 14 studies from 1980 to June 2012, demonstrating improvements of postvoid residual urine volume, reflex detrusor volume, bladder capacity, bladder compliance, and catheterization frequency ($p < 0.01$) after administration of botulinum toxin type A (BTX-A).

Wu et al. (13) searched the literature up to May 2017 and included five RCTs in their analysis. BTX-A intra-detrusorial infiltrations reduced the number of urinary incontinence episodes per day and per week compared to placebo and increased maximum cystometric capacity and decreased maximum detrusor pressure at week 6. BTX-A administration was more frequently associated with urinary tract infections.

Ni et al. (14) searched the literature up to June 2016 for papers reporting the outcomes of studies focusing on repeated BTX-A injections in adult patients with NDO. They included 18 retrospective or prospective cohort studies, but no RCT. The meta-analysis demonstrated that repeated BTX-A injections allowed sustained improvements in patients with NDO, with a stable and low rate of adverse events. *Jo et al.* (15) searched for RCTs assessing the efficacy and safety of onabotulinumtoxinA, administered in different injection sites, for treatment of OAB. The authors included studies performed in adults treated for both neurogenic detrusor overactive bladder and idiopathic OAB. Trigone-including injections demonstrated more significant improvement in symptom score, higher complete dryness rates, and lower rates of incontinence episodes compared to trigone-sparing injections. Moreover, lower detrusor pressure and higher volume at first desire to void were observed with trigone-including injection.

We added three recently published studies assessing the effect of abobotulinumtoxinA in patients with NDO on clean intermittent catheterization (49), comparing the performance of abobotulinumtoxinA by 15 intra-detrusor injections with a 30-injection regimen (43), and describing the results of the administration of onabotulinumtoxinA in Japanese patients (47). AbobotulinumtoxinA showed its efficacy in treating patients with NDO compared to placebo even when the number of injections was reduced and the efficacy of onabotulinumtoxinA was confirmed in an Asian population.

Pelvic floor muscle training (PFMT) and non-invasive electrical stimulation

A recent meta-analysis addressed studies that evaluated PFMT in multiple sclerosis patients with LUTS in the period between 1990 and 2019. *Kajbafvala et al.* (5) found that PFMT significantly reduced urinary incontinence episodes and neurogenic bladder symptoms measured according to OAB-VS scores. According to the PERFECT scheme for assessment of pelvic floor muscle function, PFMT increased the overall endurance and power of the pelvic floor musculature.

One meta-analysis by *Vecchio and coworkers* evaluated the effectiveness of *peripheral tibial nerve stimulation* (PTNS) and *pelvic floor muscle training* (PFMT) for bladder dysfunction in MS, on the basis of data retrieved up to October 2021 (6). The authors found no significant differences in voided volume after PFMT. However, according to the PERFECT scheme assessed at 3 months, endurance and fast contraction of pelvic floor muscles were significantly improved ($p = 0.002$).

Papers on PFMT (without or with electrostimulation) in patients with MS which were retrieved in our review were also previously included in these reviews.

We retrieved four additional studies reporting about PFMT in patients with PD ($n = 2$) or with post-stroke OAB ($n = 2$). Meta-analysis of two studies in patients with PD, showed that PFMT could improve OAB symptoms in PD, though the number of episodes of incontinence was not significantly decreased. In men and women with post-stroke OAB symptom scores, bladder diary parameters and pelvic floor function and strength were improved.

Gaziev et al. (7) reviewed the efficacy of TTNS in the treatment of lower urinary tract dysfunction, including overactive bladder. The authors found that TTNS was effective in 37-100% of patients with OAB. Four RCTs were retrieved; importantly, these studies did not distinguish between neurogenic and idiopathic OAB. The above cited meta-analysis by *Vecchio et al.* (6) showed significant improvements of daytime frequency, nocturia, urgency incontinence and voided volume after three months of PTNS ($p < 0.001$) in patients with MS. A significant improvement in maximum cystometric capacity was also observed. Our review added three studies evaluating the effect of PTNS in patients with PD or post-stroke OAB. Quantitative analysis of two studies comparing TTNS with sham treatment in patients with PD tentatively indicates that TTNS is more effective than sham in decreasing the number of nocturia episodes. TENS improved urinary symptoms also in patients with post-ischemic stroke by reducing urinary urgency and frequency.

Acupuncture and electroacupuncture also proved to be effective in patients with PD and in post-stroke patients. Finally, *transcutaneous electrical nerve stimulation* (TENS) was successfully used to treat post-stroke neurogenic OAB. Treatment improved voiding diary parameters and urodynamic findings and showed to be superior to anticholinergics.

Sacral neuromodulation

A systematic review evaluated the results of studies on sacral *neuromodulation* (SNM) in patients with neurogenic

lower urinary tract dysfunction. Data published between 1998 to March 2020 were retrieved. The review included retrospective or prospective clinical studies, cohort studies, and case reports. A meta-analysis of 21 studies demonstrated a 66.2% success rate of SNM test stimulation; another meta-analysis of 24 studies reported a 84.2% success rate of permanent SMN. Loss of effectiveness, infection, pain at implant site, and lead migration were observed in 4.7%, 3.6%, 3.2%, and 3.2% of cases, respectively. The clinical effect of SMN for neurogenic lower urinary tract dysfunction was comparable to the outcomes obtained in idiopathic populations.

CONCLUSIONS

Although all treatments have proven efficacy, there is no therapy that can be considered clearly superior to the others. In fact, the treatment of neurological bladder must be tailored to the individual patient, and often requires the combination of different forms of complementary treatment. Combination of different pharmacological treatments, or associating pharmacological treatments and non-pharmacological treatments, can allow reduction of the dosage of drugs, thus minimizing the side effects which represent a limitation of their usage in therapy.

A caveat: evidence from our quantitative analysis is fragmentary and does not allow to draw robust conclusions. Our data are only provisional and should be considered with caution, due to the few studies included in meta-analysis and to the small number of patients included in each study.

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