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

Rawa Bapir [1, 14], Kamran Hassan Bhatti [2, 14], Ahmed Eliwa [3, 14], Herney Andrés García-Perdomo [4, 14], Nazim Gherabi [5, 14], Derek Hennessey [6, 14], Vittorio Magri [7, 14], Panagiotis Mourmouris [8, 14], Adama Ouattara [9, 14], Gianpaolo Perletti [10, 14], Joseph Philipraj [11, 14], Konstantinos Stamatiou [12, 14], Alberto Trinchieri [13, 14], Noor Buchholz [14]

[1] Smart Health Tower, Sulaymaniyah, Kurdistan region, Iraq;
[2] Urology Department, HMC, Hamad Medical Corporation, Qatar;
[3] Department of Urology, Zagazig University, Zagazig, Sharkia, Egypt;
[4] Universidad del Valle, Cali, Colombia;
[5] Faculty of Medicine Algiers 1, Algiers, Algeria;
[6] Department of Urology, Mercy University Hospital, Cork, Ireland;
[7] ASST Nord Milano, Milan, Italy;
[8] 2nd Department of Urology, National and Kapodistrian University of Athens, Sismanoglio Hospital, Athens, Greece;
[9] Division of Urology, Souro Sanou University Teaching Hospital, Bobo-Dioulasso, Burkina Faso;
[10] Department of Biotechnology and Life Sciences, Section of Medical and Surgical Sciences, University of Insubria, Varese, Italy;
[11] Department of Urology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India;
[12] Department of Urology, Tzaneio General Hospital, 18536 Piraeus, Greece;
[13] Urology School, University of Milan, Milan, Italy;
[14] U-merge Ltd. (Urology for emerging countries), London-Athens-Dubai *

Authors 1-14 have equally contributed to the paper and share first authorship.

* *U-merge Ltd. (Urology for Emerging Countries) is an academic urological platform dedicated to facilitate knowledge transfer in urology on all levels from developed to emerging countries. U-merge Ltd. is registered with the Companies House in London/ UK. www.U-merge.com*

PICO TABLES

MIRABEGRON			
Author	Population	Intervention & Comparison	Outcome
Cho 2020	Parkinsonism patients with overactive bladder (OAB)	Mirabegron N=58 Placebo N=59 8 weeks	OABSS scores lower after mirabegron OABSS scores decreased after placebo although significantly higher than mirabegron Postvoid residual urine volume mild increase to 64 ml in the mirabegron group compared to the placebo group Adverse events in 32.3% of placebo group and in 24.1%) of mirabegron group Acute urinary retention occurred in a single case Satisfaction questionnaires no significant differences between the two groups
Khut 2017	NDO in patients with SCI and MS	Mirabegron N=32 Placebo N=34 4 wks	Mirabegron Increased volume at the first detrusor contraction (p = 0.00047) Increased bladder compliance (p = 0.0041) reduced urine leakage (p = 0.056) Not significant increase in cystometric capacity (p = 0.061) Placebo Significant changes in all the patient-reported outcomes, although less than mirabegron group The incidence of drug-related adverse events was 3.13%

No conflict of interest declared.

Moussa 2021	Patients with PD	Mirabegron N=53 Placebo N=42 12 weeks	OABSS OAB-q SF (overactive bladder questionnaire short form) significantly improved in the mirabegron group Number of micturitions, urgency episodes, incontinence episodes/ 24 h and nocturia episodes/night decreased Increase of volume voided/micturition (ml) Adverse events mild in the two groups
Ray 2017	PD patients with OAB	Mirabegron Placebo N=22	Only tolerability 2 adverse events: diarrhea and hallucinations
Welk 2018	32 patients were randomized: 16 (10 SCI and 6 MS) to placebo and 16 (9 SCI and 7 MS) patients to mirabegron	Mirabegron N=16 Placebo N=16 10 wks	MCC no significant difference between mirabegron and placebo (MIR *vs* PBP 305 *vs* 369 mL, p = 0.20) Volume at first neurogenic detrusor overactivity (NDO) no significant difference (67 *vs* 137 mL, p = 0.14) Peak pressure of NDO (69 *vs* 82 cmH2O, p = 0.25) Pad weights or voiding diary parameters no significant difference Total neurogenic bladder symptom score (29 vs 34, p = 0.047)

Cho SY, Jeong SJ, Lee S, et al. Mirabegron for treatment of overactive bladder symptoms in patients with Parkinson's disease: A double-blind, randomized placebo-controlled trial (Parkinson's Disease Overactive bladder Mirabegron, PaDoMi Study). Neurourol Urodyn. 2021; 40:286-294.

Krhut J, Borovicka V, Bilkova K, et al. Mirabegron in the treatment of neurogenic detrusor overactivity due to spinal cord injury and multiple sclerosis International Journal of Urology. 2017; 24(Suppl 1):18-19.

Moussa M, Chakra MA, Dabboucy B, et al. The safety and effectiveness of mirabegron in Parkinson's disease patients with overactive bladder: a randomized controlled trial. Scand J Urol. 2022; 56:66-72.

Ray S, Burdick D, Griffith A, Agarwal P. Preliminary report on the MAESTRO study: A pilot study of mirabegron and behavioral modification including pelvic floor exercise for overactive bladder in Parkinson's disease Movement Disorders. 2017; 32:(Suppl 2):945-946.

Welk B, Hickling D, McKibbon M, et al. A pilot randomized-controlled trial of the urodynamic efficacy of mirabegron for patients with neurogenic lower urinary tract dysfunction. Neurourol Urodyn. 2018; 37:2810-2817.

ANTICHOLINERGICS			
Amarenco 2017	Neurogenic detrusor overactivity (NDO) due to multiple sclerosis (MS) or spinal cord injury (SCI)	Oxybutynin 15 mg N=47 Solifenacin 5 mg N=48 Solifenacin 10 mg N=51 placebo N=41 4 weeks	Maximum cystometric capacity (MCC) SOL10 significantly improved change from baseline *vs* PBO ($p < 0.001$) Bladder volume at first contraction and at first leak Detrusor pressure at first leak SOL10 improved Patient perception of bladder condition SOL10 improved *vs* PBO ($p < 0.041$) Quality of life (QoL) SOL10 improved *vs* PBO Dry mouth: PBO 4.4 (22.5) Solifenacin5 4.2 (23.5) Solifenacin10 10.4 (29.3) Oxybutynin 38.7 (39.6) Other VAS scores (Constipation Blurred vision Fatigue Memory and attention) no significant difference
Fader 2007	Individuals with multiple sclerosis.	Intravesical atropine (6 mg 4 times daily) *vs* oxybutynin immediate release 57 patients crossover	Bladder capacity ATR *vs* OXY (79.6+/-89.6 *vs* 55.5+/-67.2 ml) Incontinence events and voiding frequency not statistically different Total side effect and dry mouth scores significantly better in ATR
Lackner 2008	Nursing home residents with mild to severe dementia and urge urinary incontinence	Oxybutynin N=26 Placebo N=24	Confusion Assessment Method (CAM) score from baseline no difference OXY *vs* PBO Delirium did not occur in either group Mild adverse events OXY 38.5% *vs* PBO 37.5% ($p = 0.94$)
Menarini 2006	80 patients with neurogenic detrusor overactivity	Oral trospium chloride at standard dose of 45 mg/day (3 x 15 mg) (SDG) *vs* adjustable dose group 90 or 135 mg/day (ADG) 3-5 weeks	At least two of the following three urodynamic parameters: bladder compliance 220 ml/cmH20, maximum cystometric capacity > 250 ml and maximum detrusor pressure < 40 cmH20 ADG 58% *vs* SDG 72% (p 0.23) Dry mouth (ADG 35%, SDG 37%), which never led to discontinuation of treatment Rates of other adverse events such as dry skin, dysopia, increased heart rate and gastrointestinal disorders were much lower
Schroder 2016	Neurogenic detrusor overactivity (NDO)	Intravesical oxybutynin N=18 oral oxybutynin N=17	Maximum bladder capacity IntraOXY 117 ml ($p < 0.0002$) OralOXY 18 ml ($p < 0.51$) Difference Intra *vs* oral ($p < 0.0086$) Adverse reaction less after intraOXY vision (1/10 vs. 9/14) gastrointestinal tract (8/10 *vs*. 14/14) nervous system (2/10 *vs*. 8/14) skin and subcutis (1/10 vs. 6/14) No serious adverse drug reactions were reported

Stohrer 2007	Neurogenic detrusor overactivity	Propiverine 15 mg t.i.d. N=70 *vs* Oxybutynin 5 mg t.i.d. N=61 21 days	Maximum cystometric capacity (ml) PRO 198+/-110 to 309+/-166 OXY 164+/-64 to 298+/125 Maximum detrusor pressure during the filling phase PROP 56.8+/-36.2 to 37.8+/-31.6) OXY 68.6+/-34.5 to 43.1+/-29.2 No significant differences resulted between treatment groups Adverse events PROP *vs* OXY 63.0% *vs* 77.8% dryness of the mouth 47.1% *vs* 67.2%; p = 0.02)
Stohrer 2013	Neurogenic detrusor overactivity (NDO)	Propiverine extended-release (ER) N=33 Immediate-release (IR) N=33	Reflex volume (ml) increased Leak point volume increased Maximum detrusor pressure decreased significantly in both groups, no significant intergroup differences Incontinence rate was reduced by 14% in the IR and by 39% in the ER group, the difference is significant Treatment-related adverse events manifested in 42 and 36% following propiverine IR and ER
Yonguc 2020	Parkinson disease N=23	Fesoterodine 4 mg placebo 4 weeks	N° micturitions/24 h FES 9 ± 1.1 (8–12) *vs* 8.6 ± 1.1 (7–12) 0.076 PBO 8.6 ± 1.7 (3–11) *vs* 7 ± 1.2 (5–10) < 0.001 N° urinary incontinence Urgency FES 1.9 ± 0.8 (1–4) *vs* 2.3 ± 1 (1–4) 0.076 PBO 1.8 ± 0.7 (1–4) *vs* 1.6 ± 0.8 (0–3) 0.25 Nocturia FES 0.1 ± 2.5 (0–10) *vs* 3.1± 2 (0–10) 0.997 PBO 2.7 ± 2.3 (0–9) *vs* 2.3 ± 1.7 (0–9) 0.334
Zesiewicz 2015	Idiopathic Parkinson disease N=23	Solifenacine 5-10 mg Placebo 12 weeks	N° micturitions/24 h SOL 8.78 ± 2.18 *vs* 8.00 ± 3.36 PBO 9.19 ± 3.46 *vs* 8.94 ± 3.06 N° urinary incontinence SOL 1.48 ± 2.56 *vs* 0.30 ± 0.31 PBO 1.78 ± 1.27 *vs* 1.61 ± 1.40 Urgency Nocturia SOL 2.48 ± 1.59 *vs* 2.04 ± 1.96 PBO 1.92 ± 1.14 *vs* 1.78 ± 0.88

Amarenco G, Sutory M, Zachoval R, et al. Solifenacin is effective and well tolerated in patients with neurogenic detrusor overactivity: Results from the double-blind, randomized, active- and placebo-controlled SONIC urodynamic study. Neurourol Urodyn. 2017; 36:414-421.

Fader M, Glickman S, Haggar V, et al. Intravesical atropine compared to oral oxybutynin for neurogenic detrusor overactivity: a double-blind, randomized crossover trial. J Urol. 2007; 177:208-13.

Lackner TE, Wyman JF, McCarthy TC, et al. Randomized, placebo-controlled trial of the cognitive effect, safety, and tolerability of oral extended-release oxybutynin in cognitively impaired nursing home residents with urge urinary incontinence. J Am Geriatr Soc. 2008; 56:862-70.

Menarini M, Del Popolo G, Di Benedetto P, et al. Trospium chloride in patients with neurogenic detrusor overactivity: is dose titration of benefit to the patients? Int J Clin Pharmacol Ther. 2006; 44:623-32.

Schröder A, Albrecht U, Schnitker J, et al. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: A randomized, prospective, controlled multi-center trial. Neurourol Urodyn. 2016; 35:582-8.

Stöhrer M, Mürtz G, Kramer G, et al. Propiverine compared to oxybutynin in neurogenic detrusor overactivity--results of a randomized, double-blind, multicenter clinical study. Eur Urol. 2007; 51:235-42.

Stöhrer M, Mürtz G, Kramer G, et al. Efficacy and tolerability of propiverine hydrochloride extended-release compared with immediate-release in patients with neurogenic detrusor overactivity. Spinal Cord. 2013; 51:419-23.

Yonguc T, Sefik E, Inci I, et al. Randomized, controlled trial of fesoterodine fumarate for overactive bladder in Parkinson's disease. World J Urol. 2020; 38:2013-2019.

Zesiewicz TA, Evatt M, Vaughan CP, et al. Randomized, controlled pilot trial of solifenacin succinate for overactive bladder in Parkinson's disease. Parkinsonism Relat Disord. 2015; 21:514-20.

COMPARISON OF DRUGS			
Nardulli 2012	Suprasacral spinal cord injury with urge-incontinence	Oxybutynin + Trospium chloride N=6 vs Oxybutynin + Solifenacin N=6 12 weeks	N° incontinence episodes decreased Bladder compliance, bladder capacity and volume voided increased with both treatment Well tolerated side effects were higher in patients taking oxybutyinin + solifenacin
Sakakibara 2007	Overactive bladder (OAB) in neurologic diseases	Milnacipran (SNRI), vs Paroxetine (SSRI)	Milnacipran reduced daytime urinary frequency increased bladder capacity improved quality of life Such changes were not observed after paroxetine
Vasudeva 2021	History of cerebrovascular accident (CVA) with stable status > 3 months	Darifenacin N=30 Mirabegron N=30 3 months	ICIQ bladder diary parameters improved in both arms no difference between groups No deterioration in the cognitive function MoCA-B score similar between the two arms None of the patients in either of the arms, developed intolerable adverse effects to discontinue the treatment

Nardulli R, Losavio E, Ranieri M, et al. Combined antimuscarinics for treatment of neurogenic overactive bladder. Int J Immunopathol Pharmacol. 2012; 25(1 Suppl):35S-41S.

Sakakibara R, Ito T, Uchiyama T, et al. Effects of milnacipran and paroxetine on overactive bladder due to neurologic diseases: a urodynamic assessment. Urol Int. 2008; 81:335-9.

Vasudeva P, Kumar A, Yadav S, et al. Neurological safety and efficacy of darifenacin and mirabegron for the treatment of overactive bladder in patients with history of cerebrovascular accident: A prospective study. Neurourol Urodyn. 2021; 40:2041-2047.

CANNABINOIDS			
Freeman 2006	Patients with MS	Cannabis extract N=88 Δ9tetrahydrocannabinol (THC) N=86 *vs* placebo N=81	Incontinence episode rates 38 *vs* 33 *vs* 18% Significant difference with placebo P < 0.005 (Cannabis) P < 0.039 (THC) The drug appeared to be well tolerated Dyssynergia in only two patients with Δ9 -THC compared with three taking placebo
Kavia 2010	Subjects with MS and overactive bladder (OAB)	Sativex (nabiximols), an endocannabinoid system modulator N=56 *Vs* Placebo N=62 8 weeks	Endpoints were in favor of Sativex vs PBO - episodes of nocturia (-0.28, p < 0.010) - overall bladder condition (1.16, p < 0.001) - voids/day (0.85, p < 0.001) - patient's Global Impression of Change (p < 0.005) - daytime voids (-0.57, p < 0.044) Adverse effects dizziness (17.9% Sativex, 7.4% placebo) disorientation (6% Sativex *vs*. 1.5% placebo) dissociation (6% Sativex vs. 0% placebo) other CNS-type below 5% in the Sativex group

Freeman RM, Adekanmi O, Waterfield MR, et al. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct. 2006; 17:636-41.

Kavia RB, De Ridder D, Constantinescu CS, et al. Randomized controlled trial of Sativex to treat detrusor overactivity in multiple sclerosis. Mult Scler. 2010; 16:1349-59.

INTRAVESICAL INSTILLATION			
De Seze 1998	Spinal cord lesions by MS (12) or trauma (8) with urge incontinence	One intravesical instillation 30 mg Capsaicin in 100 ml 30% Ethanol N=10 or 100 ml 30% ethanol alone N=10	Capsaicin decrease in 24-h voiding frequency (9.3 ± 6.1 to 6.7 ± 3.8, p < 0.016) decrease in leakages 3.9 ± 1.6 to 0.6 ± 0.8 (p < 0.0008) increase maximum cystometric capacity 169 ± 68 to 299 ± 96 ml (p < 0.01) decrease maximum detrusor pressure 77 ± 24 to 53 ± 27 cm H2O No significant changes in the control group Side effects (suprapubic pain, sensory urgency, flushes, hematuria, autonomic hyperreflexia) in 7 subjects of each group
De Seze 2006	Neurogenic detrusor overactivity (NDO) in SCI and MS	Capsaicin in a glucidic solution N=17 or glucid solvent alone N=16	Both groups decreased daily leakage and voiding increase in security delay increase MCC improvement quality of life no improvement in SG no improvement on D90 No significant differences between groups regarding prevalence, duration, or intensity of side effects, except for short duration pubic pain during instillation more often reported in CG (58.8%) than in SG (12.5%) (p < 0.01)
Lazzeri 2006	Self-catheterization for neurogenic detrusor overactivity incontinence	Intravesical instillation at the first morning catheterization for 10 days 1 mg of nociceptin/ orphanin FQ N=9 vs saline N=9	Nociceptin/orphanin FQ urine leakage from 2.18 to 0.94 (p < 0.05) voiding diary bladder capacity from 171 to 294 Placebo group no significant changes no significant side effects

De Sèze M, Wiart L, Joseph P-A, et al. Capsaicin and neurogenic detrusor hyperreflexia: A double-blind placebo- controlled study in 20 patients with spinal cord lesions Neurourology and Urodynamics. 1998; 17:5(513-523) Cited by: 97

de Sèze M, Gallien P, Denys P, et al. Intravesical glucidic capsaicin versus glucidic solvent in neurogenic detrusor overactivity: a double blind controlled randomized study. Neurourol Urodyn. 2006; 25:752-7.

Lazzeri M, Calò G, Spinelli M, et al. Daily intravesical instillation of 1 mg nociceptin/orphanin FQ for the control of neurogenic detrusor overactivity: a multicenter, placebo controlled, randomized exploratory study. J Urol. 2006; 176:2098-102.

INTRADETRUSOR INJECTION WITH BOTOLINUM TOXIN COMPARED TO PLACEBO			
Chancellor 2013	Urinary incontinence (UI) due to neurogenic detrusor	OnabotulinumtoxinA (200 U) N=135 onabotulinumtoxiA (300 U) N=132 or placebo (0.9% saline) N=149	I-QOL Questionnaire total score OAB-PSTQ Patient Global Assessment greater improvement in both onabotulinumtoxinA-treated groups ($p < 0.001$) *vs* placebo
Cruz 2011	Incontinent patients with NDO	OnabotulinumtoxnA 200 U (n = 92) onabotulinumtoxinA 300 U (n = 91) placebo (n = 92), Patients received 30 intradetrusor injections avoiding the trigone	At week 6 onabotulinumtoxinA 200 U and 300 U significantly reduced UI episodes per week compared with placebo MCC, PdetmaxIDC, and I-QOL at week 6 were significantly greater with both onabotulinumtoxinA doses than with placebo ($p < 0.001$) Adverse events: localised urologic events (urinary tract infections and urinary retention, which were dose related in patients not using clean intermittent catheterisation at baseline) Significant increases in postvoid residual were observed in patients not using CIC prior to treatment 12%, 30%, and 42% of patients in the placebo, 200-U, and 300-U groups, respectively, initiated CIC posttreatment
Del Popolo 2016	MS patients not catheterizing at baseline inadequaely managed by ≥ 1 anticholinergic	Intradetrusor injections of onabotulinumtoxinA 100U (N=66) or placebo (N=78) 30 injections each of 1mL via cystoscop, avoiding the trigone	Assessments at week 6 post-treatment OnabotulinumtoxinA 100U - reduced UI episodes/day - improved maximum cystometric capacity -improved maximum detrusor pressure during first involuntary detrusor contraction Adverse events: urinary tract infection, elevated residual urine volume, and urinary retention
Denys 2017	Adult patients with NDO urinary incontinence resulting from SCI or MS	AbobotulinumtoxinA (Dysport1) 15 intra-detrusor injections of Dysport 750 U N=16 or placebo N=7 30 injections of Dysport 750 U N=17 or placebo N=7	Both 15 and 30 injections administration decreased daily IEF Improved significantly urodynamic parameters (maximum cystometric capacity, maximum detrusor pressure and volume at first contraction) in the Dysport groups compared with placebo ($p < 0.05$)
Ehren 2007	Urinary leakage due to spinal cord injury, myelomeningocele, trauma at birth, multiple sclerosis and myelitis of another cause	31 patients randomized single injection of 500U of botulinum toxin A (BTX-A; Dysport) or placebo	At week 6 Cystometric capacity significantly higher ($p < 0.001$) Lower maximum detrusor pressure and frequency of urinary leakage ($p < 0.01$) in the BTX-A group compared to the placebo group Improved quality-of-life parameters in the BTX-A group compared to the placebo group
Ginsberg 2012	416 patients with NDO and urinary incontinence (14 or more episodes per week) resulting from MS (227) and SCI (189)	OnabotulinumtoxinA at a dose of 200 U in N=135 OnabotulinumtoxinA 300 U N=132 Placebo N=140	At week 6 decreased mean urinary incontinence Naximum cystometric capacity, maximum detrusor pressure during the first involuntary detrusor contraction and Incontinence Quality of Life score significantly improved with respect to placebo group

Herschorn 2011	NDO secondary to SCI or MS	OnabotulinumtoxinA 300 U N=28 or placebo N=29 At 30 intradetrusor sites, sparing the trigone	At week 6 Lower daily frequency of urinary incontinence episodes for onabotulinumtoxinA than placebo Improved urodynamic and quality of life parameters for treatment vs placebo Most common adverse was urinary tract infection
Honda 2021	Japanese patients with NDP caused by SCI or MS	OnabotulinumtoxinA 200 U onabotulinumtoxinA (N = 11) placebo (N = 10)	Number of urinary incontinence episodes per day greater reduction than placebo difference between the groups at week 6 of 3.02 (95% confidence interval 5.85 to 0.19). Greater improvements in urodynamic assessments for treatment group Adverse events: hematuria, urinary retention, urinary bladder hemorrhage, autonomic dysreflexia and epididymitis. Most events were deemed mild or moderate
Kennelly 2022	SCI or clinically stable MS with NDO performing clean intermittent catheterization inadequately managed with oral therapy	AbobotulinumtoxinA injections of aboBoNT-A 600 U (n = 162) or 800 U (n = 161) or placebo (n = 162) into the detrusor muscle.	At week 6 - reduced NDOI episodes per week in both aboBoNT-A groups versus placebo (both p < 0.001) - significantly increased volume per void and improved UI-related QoL in the aboBoNT-A groups versus placebo - bladder capacity and detrusor pressure significantly improved in aboBoNT-A groups versus placebo Adverse events:symptomatic urinary tract infection
Schurch 2005	NDO of predominantly SCI origin	Botulinum toxin type A (BTX-A) 200 U N=19 300 U N=19 Placebo N=21	Decreased incontinence episodes in the 2 BTX-A groups (p < 0.05) but not in the placebo group improved urodynamics and quality of life in the BTX-A groups No safety concerns
Schurch 2007 Evaluation of QoL in the same series of *Schurch 2005*	NDO of predominantly SCI origin	single dose of BoNTA (200 U or 300 U, Botox1) or placebo	I-QOL scores increased significantly with BoNTA 300 U and BoNTA 200 U compared with placebo at all time points (p < 0.05)
Sussman 2013	MS or SCI	OnabotulinumtoxinA 200 U N=92 300 U N=91 Placebo N= 92	At 6 and 12 weeks I-QOL total score significantly improved with both onabotulinumtoxinA 200 U and 300 U versus placebo (p < 0.001) Improved OAB-PSTQ in satisfaction versus placebo (p < 0.001)

Del Popolo G, Denys P, Keppenne V, et al. Efficacy and safety of onabotulinumtoxina 100u for treatment of urinary incontinence due to neurogenic detrusor overactivity in non-catheterising multiple sclerosis patients Neurourology and Urodynamics. 2016; 35(Suppl 3):S53-S54.

Chancellor MB, Patel V, Leng WW, et al. OnabotulinumtoxinA improves quality of life in patients with neurogenic detrusor overactivity. Neurology. 2013; 81:841-8.

Cruz F, Herschorn S, Aliotta P, et al. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2011; 60:742-50.

Denys P, Del Popolo G, Amarenco G, et al. Efficacy and safety of two administration modes of an intra-detrusor injection of 750 units dysport® (abobotulinumtoxinA) in patients suffering from refractory neurogenic detrusor overactivity (NDO): A randomised placebo-controlled phase IIa study. Neurourol Urodyn. 2017; 36:457-462.

Ehren I, Volz D, Farrelly E, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: a randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol. 2007; 41:335-40.

Ginsberg D, Gousse A, Keppenne V, et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012; 187:2131-9.

Herschorn S, Gajewski J, Ethans K, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: a randomized, double-blind trial. J Urol. 2011; 185:2229-35.

Honda M, Yokoyama O, Takahashi R, et al. Botulinum toxin injections for Japanese patients with urinary incontinence caused by neurogenic detrusor overactivity: Clinical evaluation of onabotulinumtoxinA in a randomized, placebo-controlled, double-blind trial with an open-label extension. Int J Urol. 2021; 28:906-912.

Kennelly M, Cruz F, Herschorn S, et al. Efficacy and Safety of AbobotulinumtoxinA in Patients with Neurogenic Detrusor Overactivity Incontinence Performing Regular Clean Intermittent Catheterization: Pooled Results from Two Phase 3 Randomized Studies (CONTENT1 and CONTENT2) European Urology 2022.

Schurch B, De Sèze M, Denys P, et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: Results of a single treatment, randomized, placebo controlled 6-month study J Urol. 2005; 174:196-200.

Schurch 2007.

Evaluation of QoL in the same series of Schurch 2005.

Sussman D, Patel V, Del Popolo G, et al. Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurourol Urodyn. 2013; 32:242-9.

COMPARISON OF TRIGONE-INCLUDING AND TRIGONE EXCLUDING BOTOLINUM TOXIN INJECTIONS			
Abdel-Meguid 2010	Refractory NDO by SCI	300 U botulinum toxin-A intradetrusor injections excluding the trigone (detrusor arm) N=18 or 200 U intradetrusor plus 100 U intratrigonal injections (combined arm) N=18	Detrusor *vs* combined arm at week 8 - incontinence decreased by 52.4% *vs* 80.9% - complete dryness was achieved in 33.3% *vs* 66.7% - quality of life score decreased by 46.76% *vs* 48.13% - 66.2% *vs* 68.4% for maximum cystometric capacity (p 0.22) - 42.3% *vs* 41.9% for maximum detrusor pressure (p 0.21)
Hui 2016	NDO with incontinence	160 U intradetrusor and 40 U intratrigonal injections (experimental) N=47 *Vs* 200 U BTX-A intradetrusor injections excluding the trigone (the control group) N=44	At 12 weeks better improvement in the combined intratrigonal/intradetrusor group compared with intradetrusor group for I-QoL (p = 0.01) urinary incontinence episodes (p = 0.01) complete dryness (p = 0.03) voiding volume (p = 0.02) Pdetmax (p = 0.04) VFIDC (p = 0.02) duration of first detrusor contraction (p = 0.03) number of patients with detrusor contraction (p = 0.02) In both the groups, no patients developed VUR

COMPARISON OF DIFFERENT DOSE OF BOTULINUM TOXIN INJECTIONS			
Grise 2010	UI resulting from NDO and were refractory to oral anticholinergicson clean intermittent self-catheterisation	Botulinum toxin type A (BoNTA) Intradetrusor injection of 500 U or 750 U of BoNTA 500 U (n = 39) or 750 U (n = 38)	Complete continence in 56.4% and 73.7% patients receiving 500 U or 750 U of BoNTA, (p = 0.056) No statistically significant differences in terms of clinical and urodynamic variables and QoL between groups

Abdel-Meguid TA. Botulinum toxin-A injections into neurogenic overactive bladder--to include or exclude the trigone? A prospective, randomized, controlled trial. J Urol. 2010; 184:2423-8.

Hui C, Keji X, Chonghe J, et al. Combined detrusor-trigone BTX-A injections for urinary incontinence secondary to neurogenic detrusor overactivity. Spinal Cord. 2016; 54:46-50.

Grise P, Ruffion A, Denys P, et al. Efficacy and tolerability of botulinum toxin type a in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: Comparison of two doses Eur Urol 2010; 58:759-766.

TIBIAL NERVE STIMULATION *VS* SHAM/GENERAL ADVICE			
Araujo 2020	Overactive bladder (OAB) in women with Parkinson's disease (PD)	Home TTNS stimulation N=15 *vs* sham N=15 12 wks	TTNS reduced night-time urinary frequency, urinary urgency, urgency incontinence episodes use of pads OAB-V8 and King's Health Questionnaire scores In a 30-day and 90-day follow-up, 8 (53.3%) and 5 (33.3%) stimulation patients, respectively, reported full maintenance of symptom relief
Monteiro 2014	Neurogenic overactive bladder secondary to ischemic stroke	TTNS Twice weekly *Vs* General advice and stretching sessions 6 weeks	45 days and 12 months after treatment TENS improved urinary symptoms (urinary urgency and frequency) reported subjective improvement after treatment This effect persisted after 12 months of follow-up
Perissinotto 2015	LUTS with Parkinson's disease	TTNS N=8 *vs* Sham N=5 Twice weekly 5 weeks	At 5 weeks TTNS reductions in the number of urgency episodes ($p = .004$) reductions in nocturia episodes ($p < .01$) better OAB-V8 and ICIQ-SF scores ($p < .01$) improvements in intravesical volume at strong desire to void ($p < .05$) improvement volume at urgency ($p < .01$) when compared to subjects in the sham treatment group
TIBIAL NERVE STIMULATION *VS* PFMT			
Gaspard 2014	LUTS and MS	TTNS N=15 *Vs* pelvic floor muscle training N=16	PFMT significantly improved quality of life (SF-Qualiveen) overactive bladder symptom score (USP) rate of urgency episodes were (respectively $p = 0.004$, $p = 0.002$, $p = 0.006$) TTNS significantly improved same parameters (respectively $p = 0.001$, $p = 0.001$, $p = 0.031$) No difference between groups was observed
TIBIAL NERVE STIMULATION *VS* ANTICHOLINERGICS			
Eftekhar 2014	50 women neurologic bladder	TTNS + tolterodine 4 mg N=23 *vs* tolterodine 4 mg N=17 2 in PTNS and 8 in control group withdrew from the study	FSFI (Female sexual function Index) was significantly different before and after treatment in each group ($p < 0.001$), but no difference was observed between the two groups Urgency became significantly different after treatment between two groups with no side effects
Zonic-Imamovic 2019	Multiple sclerosis with OAB	TTNS N=30 *vs* oxybutynin 5 mg x 2 N=30 3 months	Anticholinergic therapy statistically significant improvement in all symptoms and quality of life ($p < 0.001$) side effects such as dry mouth were observed in about 35% TTNS reduced urinary symptoms improved quality of life, with less statistical significance ($p < 0.05$)

Araujo TG, Schmidt AP, Sanches PRS, et al. Transcutaneous tibial nerve home stimulation for overactive bladder in women with Parkinson's disease: A randomized clinical trial. Neurourol Urodyn. 2021; 40:538-548.

Monteiro ÉS, de Carvalho LB, Fukujima MM, et al. Electrical stimulation of the posterior tibialis nerve improves symptoms of poststroke neurogenic overactive bladder in men: a randomized controlled trial. Urology. 2014; 84:509-14.

Perissinotto MC, D'Ancona CA, Lucio A, et al. Transcutaneous tibial nerve stimulation in the treatment of lower urinary tract symptoms and its impact on health-related quality of life in patients with Parkinson disease: a randomized controlled trial. J Wound Ostomy Continence Nurs. 2015; 42:94-9.

Gaspard L, Tombal B, Opsomer RJ, et al. Kinésithérapie et symptômes du bas appareil urinaire chez des patients atteints de la sclérose en plaques: étude contrôlée randomisée [Physiotherapy and neurogenic lower urinary tract dysfunction in multiple sclerosis patients: a randomized controlled trial]. Prog Urol. 2014; 24:697-707.

Eftekhar T, Teimoory N, Miri E, et al. Posterior tibial nerve stimulation for treating neurologic bladder in women: a randomized clinical trial. Acta Med Iran. 2014; 52:816-21.

Zonic-Imamovic M, Imamovic S, Cickušic A, et al. Effects of Treating an Overactive Urinary Bladder in Patients with Multiple Sclerosis. Acta Med Acad. 2019; 48:271-277.

ACUPUNCTURE			
Chen 2012	60 cases OAB with Parkinson's disease	Acupuncture + tolterodine 1 mg x 2 N=30 vs Tolterodine mg x 2 N=30	Improved ($p < 0.01$) More improved in group A ($p<0.05$) Frequency of urination of 24 hours frequency of incontinence of 24 h average urine volume UPDRSIII score in group A was superior to that in group B ($p < 0.05$) The adverse reactions in group A were less than those in group B
Chen 2021	Post-stroke subjects with OAB	Electroacupuncture N=16 vs Standard care N=18 4 wks	Perceived severity of OAB symptoms (OABSS) at week 5 ($p < 0.034$) at week 8 ($p < 0.021$) No significant differences in bladder diary parameters or SSQoL The EA treatment was well tolerated by the post-stroke subjects

Chen YL, Feng WJ, Zhang XL. Parkinson's disease combined with overactive bladder syndrome treated with acupuncture and medication. Zhongguo Zhen Jiu. 2012; 32:215-8.

Chen H, Wang C, Zhou M, et al. Electroacupuncture for post-stroke overactive bladder: a multi-centre pilot randomized controlled trial. Acupunct Med. 2021; 39:175-183.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) NEUROMUSCOLAR ELECTRICAL STIMULATION (NMES)			
Guo 2014	Urinary incontinence post-stroke	TENS N=32 or basic therapy N=29 2 months 70 Hz frequency, 70 μS pulse duration, unidirectional square wave for 30 minutes once a day	TENS significantly improved daily micturition nocturia urgent urination urge UI compared to the control group ($p < 0.05$) TENS improved self-care ability of daily living TENS improved maximum cystometry volume flow rate pressure of detrusor in the end of the filling phase
Guo 2018	Urinary incontinence post-stroke	Neuromuscular electrical stimulation (NMES) N=41 or sham N=41 10 wks 50Hz frequency, 250ms pulse, 10 seconds on and 30 seconds off for 30 minutes	NMES therapy better efficacy in - urodynamic values ($p < 0.01$) - OABSS ($p < 0.01$) - ICIQ-SF ($p < .01$) - BI ($p < .01$) compared with sham NMES No adverse events were recorded in both groups.
Liu 2016	Urinary incontinence caused by stroke	20-Hz TENS group N=27 75-Hz TENS group N=27 control group N=27 30 min/day for 90 days biphasic square wave with pulse durations of 150 μs and pulse frequency at 20 Hz	75-Hz group Overactive Bladder Symptom Scores Barthel Index totals urodynamic values voiding diary parameters were statistically improved compared with the no-treatment group ($p < 0.05$), but the results were significantly inferior to those of the 20-Hz group ($p < 0.05$)
Liu 2022	Neurogenic OAB refractory to pharmacotherapy	83 pts randomized to TENS *Vs* anticholinergic drugs 90 days Biphasic square waves with pulse durations of 150 μsecs and pulse frequencies of 20 Hz or 75 Hz	TENS decreased Overactive Bladder Symptom scores ($p < 0.001$) improved half of the Medical Outcomes Study 36-Item Short-Form Health Survey score ($p < 0.05$) improved significantly voiding diary parameters ($p < 0.05$) and urodynamic values ($p < 0.05$)

Guo ZF, Liu Y, Hu GH, et al. Transcutaneous electrical nerve stimulation in the treatment of patients with poststroke urinary incontinence. Clin Interv Aging. 2014; 9:851-6.

Guo GY, Kang YG. Effectiveness of neuromuscular electrical stimulation therapy in patients with urinary incontinence after stroke: A randomized sham controlled trial. Medicine (Baltimore). 2018; 97:e13702.

Liu Y, Xu G, Luo M, Teng HF. Effects of Transcutaneous Electrical Nerve Stimulation at Two Frequencies on Urinary Incontinence in Poststroke Patients: A Randomized Controlled Trial. Am J Phys Med Rehabil. 2016; 95:183-93.

Liu Y, Xu G, Geng J. Efficacy of Transcutaneous Electrical Nerve Stimulation in the Management of Neurogenic Overactive Bladder: A Randomized Controlled Trial. Am J Phys Med Rehabil. 2022; 101:2-10.

PELVIC FLOOR MUSCLE TRAINING			
Khan 2010	Persons with multiple sclerosis	Bladder rehabilitation programme N=24 *vs* controls N=34	Compared with controls, the treatment group showed improvement in UDI6 total scores ($p < 0.001$) Significant change scores were also obtained for the NDS, AUA total and AUA QoL scores (all $p < 0.001$)
Lucio 2011	Women with multiple sclerosis	Pelvic floor muscle training (PFMT) N=18 *vs* sham procedure N=17	fewer storage and voiding symptoms in the treatment group than the sham group Significant improvements in the treatment group: Overactive Bladder Questionnaire, International Consultation on Incontinence Questionnaire Short Form General Quality of Life Specific Impact of Urinary Problems domains of the Qualiveen questionnaire
McDonald 2020	troublesome LUTS in PD	Bladder training N=20 *vs* Conservative advice N=18	At 12 weeks BT compared to CA superiority on patient perception of improvement ($p = 0.001$) significantly greater reductions in number of voids in 24 hours (mean decrease 2.3 ± 0.8 voids *vs* 0.3 ± 0.5 [$p < 0.05$]) greater reductions in interference with daily life (2.1 ± 0.8 point improvement *vs* 0.3 ± 0.7 point deterioration [$p < 0.05$]) BT was not associated with change in urgency episodes (mean change 2.4 ± 1.5 urgency episodes *vs* 3.5 ± 1.5 [p NS])
Tibaek 2005	Women with urinary incontinence post-stroke	Pelvic floor muscle training (PFMT) N=12 *vs* control N=12 12 weeks	Improved - daytime voiding (Treatment Group/Control Group: 7/8 at pre-test, 6/9 at post-test (median values), $p < 0.018$) -24-hr pad test (Treatment Group/Control Group: 8/12 to 2/8 g $p < 0.013$) - dynamic endurance of pelvic floor muscle (Treatment Group/Control Group: 11/20 to 20/8 contractions of Pelvic Floor Muscle, $p < 0.028$) - voiding in daytime (decreased from seven to six, P ¼ 0.036) - pelvic floor muscle function ($p < 0.034$), strength ($p < 0.046$), static endurance increased from 9 to 30 sec ($p < 0.028$) - dynamic endurance increased from 11 to 20 contractions ($p < 0.020$) was also demonstrated within the Treatment Group, but not in the Control Group
Tibaek 2017	Men with poststroke	Pelvic floor muscle training (PFMT) N=15 *vs* controls N=15 12 weeks	DAN-PSS-1 symptom score improved ($p < 0.01$) in the treatment group from pretest to posttest, but not in the control group DAN-PSS-1 total score improved statistically significantly in both groups from pretest to posttest (treatment group: $p < .01$; control group: $p = .03$) Median voiding frequency per 24 hours decreased from 11 at pretest to 7 (36%; $p = .04$) at posttest and to 8 (27%; $p = .02$) at follow-up in treatment group, although not statistical significantly more than the control group Pelvic floor muscle function ($p < .01$) and strength ($p < .01$) improved from pretest to posttest and from pretest to follow-up ($p = .03$; $p < .01$) in the treatment group but not the control group Compared with the control group the pretest to posttest was significantly better in the treatment group ($p = .03$)
Vaughan 2019	With Parkinson's and greater than or equal to 4 incontinence episodes weekly	Behavioral therapy including pelvic floor muscle training (PFMT) N=26 *Vs* Control N=21	Behavioral therapy participants reported statistically similar reduction in OAB symptoms compared to control (-3.1 ± 2.8 *vs* -1.9 ± 2.2, $p = 0.19$); however quality of life (-22.6 ± 19.1 *vs* -7.0 ± 18.4, $p = 0.048$) and bother (-12.6 ± 17.2 *vs* -6.7 ± 8.8, $p = 0.037$) improved significantly more with behavioral therapy

Khan F, Pallant JF, Pallant JI, et al. A randomised controlled trial: Outcomes of bladder rehabilitation in persons with multiple sclerosis Journal of Neurology, Neurosurgery and Psychiatry. 2010; 81:9 (1033-1038).

Lúcio AC, Perissinoto MC, Natalin RA, et al. A comparative study of pelvic floor muscle training in women with multiple sclerosis: its impact on lower urinary tract symptoms and quality of life. Clinics (Sao Paulo). 2011; 66:1563-8.

McDonald C, Rees J, Winge K, et al. Bladder training for urinary tract symptoms in Parkinson disease: A randomized controlled trial. Neurology. 2020; 94:e1427-e1433.

Tibaek S, Gard G, Jensen R. Pelvic floor muscle training is effective in women with urinary incontinence after stroke: a randomised, controlled and blinded study. Neurourol Urodyn. 2005; 24:348-57.

Tibaek S, Gard G, Dehlendorff C, et al. Is Pelvic Floor Muscle Training Effective for Men With Poststroke Lower Urinary Tract Symptoms? A Single-Blinded Randomized, Controlled Trial. Am J Mens Health. 2017; 11:1460-1471.

Vaughan CP, Burgio KL, Goode PS, et al. Behavioral therapy for urinary symptoms in Parkinson's disease: A randomized clinical trial. Neurourol Urodyn. 2019; 38:1737-1744.

PFMT + ELECTROTHERAPY			
Botini 2019	Women with relapsing remitting form of MS presenting LUTS for at least 6 months	Pelvic floor muscle training (PFMT) + intravaginal electrostimulation N=10 *vs* home PFMT N=10 6 months	Improvement of OAB-V8 questionnaire and it was significant between groups ($p < 0.001$) Better results of the PERFECT scheme assessment of PFMT + electrostimulation compared to PFMT in all domains
Ferreira 2015	Women with multiple sclerosis	Pelvic floor muscle training (PFMT) + electrotherapy N=12 *Vs* PFMT alone N=12 6 months	Improvement in both groups of quality-of-life (Qualiveen Questionnaire) ($p = 0.001$) overactive bladder ($p = 0.001$) (OAB-V8), perineal contraction (PERFECT scheme) ($p = 0.004$) level of anxiety ($p = 0.001$) and depression ($p = 0.001$) (Hospital Anxiety and Depression scale) association of electrotherapy increased the improvement in term of overactive bladder ($p = 0.039$) perineal contraction ($p = 0.001$)
Silva Ferreira 2019	Lower urinary tract symptoms in multiple sclerosis	Pelvic floor muscle training (PFMT) plus vaginal electrostimulation N=15 versus home PFMT N=15	Improvement in both groups overactive bladder score (OAB) quality of life (Qualiveen) Participants undergoing PFMT plus electrotherapy presented greater improvement on contraction of the perineal musculature and quality of life
r			
Lucio 2016	MS and LUTS	PFMT (with EMG biofeedback) N=10 PFMT+intravaginal NMES N=10 PFMT+TTNS N=10 12 weeks	All groups: reductions in pad weight, urgency and urinary incontinence rate, improvement in all domains of the PFM assessment, and lower OAB-V8 and ICIQ-SF scores Group 2 (PFMT+NMES) significantly greater improvement in PFM tone, flexibility, ability to relax PFM, and OAB-V8 scores when compared to subjects in groups 1 and 3

Botini D, Lucio A, Domingos J, et al. Pelvic floor muscle training in the treatment of lower urinary tract symptoms in women with multiple sclerosis and myelopathy associated with HTLV-I (HAM/TSP): A randomized controlled trial Neurourology and Urodynamics. 2019; 38(Suppl 3): S455-.

Ferreira AP, Pegorare AB, Salgado PR, et al. Impact of a Pelvic Floor Training Program Among Women with Multiple Sclerosis: A Controlled Clinical Trial. Am J Phys Med Rehabil. 2016; 95:1-8.

Silva Ferreira AP, de Souza Pegorare ABG, Miotto Junior A, et al. A Controlled Clinical Trial on the Effects of Exercise on Lower Urinary Tract Symptoms in Women With Multiple Sclerosis. Am J Phys Med Rehabil. 2019; 98:777-782.

Lúcio A, D'Ancona CA, Perissinotto MC, et al. Pelvic Floor Muscle Training With and Without Electrical Stimulation in the Treatment of Lower Urinary Tract Symptoms in Women With Multiple Sclerosis. J Wound Ostomy Continence Nurs. 2016; 43:414-9.

OTHERS			
Witte 2017	Patients with advanced PD	Globus pallidus pars interna (GPi) deep brain stimulation (DBS) N=65 *vs* subthalamic nucleus (STN) DBS N=63 12 months	Urinary incontinence and frequency improved after both GPi DBS and STN DBS (statistically significant for the STN DBS group, p = 0.004) Nocturia and urinary incontinence did not improve significantly after any type of DBS
Moussa 2021	PD-related OAB symptoms	intradetrusor adipose stem cells (ADSC) injections N=6 or single injection of saline 6 months	ADSC injection significantly decreased symptom score (OABSS, OAB-q SF symptom bother score, OAB-q SF total HRQL score) and voiding diary parameters (micturition/24 h, urgency episodes/24, leaks/24 h No serious adverse events reported in the treatment or placebo group

Witte LP, Odekerken VJJ, Boel JA, et al. NSTAPS study group. Does deep brain stimulation improve lower urinary tract symptoms in Parkinson's disease? Neurourol Urodyn. 2018; 37:354-359.

Moussa M, Abou Chakra M, Dabboucy B, et al. Single intradetrusor injection of autologous adipose-derived stem cells in Parkinson's disease patients with overactive bladder: A pilot study Neurourology and Urodynamics. 2021; 40(Suppl 2):S93-S95.

Risk of Bias

MIRABEGRON

Studies	D1	D2	D3	D4	D5	Overall
Cho 2020	+	+	+	+	+	+
Moussa 2021	+	+	+	+	+	+
Krhut 2017	+	+	!	+	+	-
Ray 2017	+	+	+	+	+	+
Welk 2018	+	!	+	!	+	!

+	Low risk
!	Some concerns
-	High risk

ANTICHOLINERGICS

Studies	D1	D2	D3	D4	D5	Overall
Amarenco 2021	+	+	+	+	+	+
Fader 2007	+	+	+	+	!	!
Lackner 2008	+	+	+	+	+	+
Menarini 2006	+	+	+	+	+	+
Schroder 2016	+	+	+	+	!	!
Stohrer 2007	+	+	+	+	+	+
Stohrer 2013	+	+	+	+	+	+
Yonguc 2020	+	+	+	+	!	+
Zesiewicz 2015	+	+	+	+	+	+

+	Low risk
!	Some concerns
-	High risk

COMPARISON OF DRUGS

Studies	D1	D2	D3	D4	D5	Overall
Nardulli 2012	+	+	!	!	+	-
Sakakibara 2007	+	+	+	+	!	!
Vasudeva 2021	+	!	!	+	+	-

+	Low risk
!	Some concerns
-	High risk

CANNABINOIDS

Studies	D1	D2	D3	D4	D5	Overall
Freeman 2006	!	+	+	+	+	!
Kavia 2010	+	+	+	+	!	!

+ Low risk
! Some concerns
- High risk

INTRAVESICAL INSTILLATIONS

Studies	D1	D2	D3	D4	D5	Overall
De Seze 1998	!	+	!	!	+	-
De Seze 2006	+	+	!	+	+	!
Lazzeri 2006	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

INTRADETRUSOR INJECTION WITH BOTOLINUM TOXIN

Studies	D1	D2	D3	D4	D5	Overall
Chancellor 2013	+	+	+	+	+	+
Cruz 2011	+	+	+	+	+	+
Del Popolo 2016	+	+	+	+	+	+
Denys 2017	+	+	+	+	+	+
Ehren 2007	!	+	!	!	!	-
Ginsberg 2012	+	+	+	+	+	+
Herschorn 2011	+	+	+	+	+	+
Honda 2021	+	+	+	+	+	+
Kennelly 2022	+	+	+	+	+	+
Schurch 2005	+	+	+	+	+	+
Schurch 2007	+	+	+	+	+	+
Sussman 2013	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

COMPARISON OF TRIGONE-INCLUDING AND TRIGONE EXCLUDING BOTOLINUM TOXIN INJECTIONS & COMPARISON OF DIFFERENT DOSE OF BOTULINUM TOXIN INJECTIONS

Studies	D1	D2	D3	D4	D5	Overall		
AbdelMeguid 2010	+	+	+	+	+	+	+	Low risk
Grise 2010	+	+	+	+	+	+	!	Some concerns
Hui 2016	+	+	+	+	+	+	-	High risk

TIBIAL NERVE STIMULATION VS SHAM/GENERAL ADVICE

Studies	D1	D2	D3	D4	D5	Overall		
Araujo 2020	+	+	+	+	+	+	+	Low risk
Monteiro 2014	+	+	!	+	+	!	!	Some concerns
Perissinotto 2015	+	+	+	+	+	+	-	High risk

TIBIAL NERVE STIMULATION VS PFMT OR ANTICHOLINERGIC

Studies	D1	D2	D3	D4	D5	Overall		
Gaspard 2014	!	-	+	+	+	-	+	Low risk
ZonicImamovic 2019	!	-	!	+	+	-	!	Some concerns
Eftekhar 2014	!	-	!	!	+	-	-	High risk

ACUPUNCTURE

Studies	D1	D2	D3	D4	D5	Overall		
Chen 2012	!	-	!	+	+	-	+	Low risk
Chen 2021	!	-	+	+	+	-	!	Some concerns
							-	High risk

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) - NEUROMUSCOLAR ELECTRICAL STIMULATION (NMES)

Studies	D1	D2	D3	D4	D5	Overall		
Guo 2014	+	+	+	+	+	+	+	Low risk
Guo 2018	+	+	+	+	+	+	!	Some concerns
Liu 2016	!	+	+	+	+	!	-	High risk
Liu 2022	!	+	+	+	+	!		

PFMT + ELECTROTHERAPY

PFMT VS PFMT+TTNS VS PFMT+TENS

Studies	D1	D2	D3	D4	D5	Overall		
Botini 2019	-	-	-	+	+	-	+	Low risk
Ferreira 2015	-	-	+	+	+	-	!	Some concerns
Khan 2010	+	-	+	+	+	!	-	High risk
Lucio 2011	+	+	-	+	+	!		
McDonald 2020	+	-	+	+	+	!		
Silva Ferreira 2019	+	-	+	+	+	!		
Tibaek 2005	+	-	+	+	+	!		
Tibaek 2017	+	-	+	+	+	!		
Vaughan 2019	+	-	+	+	+	!		
Lucio 2016	!	+	+	+	+	!		

OTHERS

Studies	D1	D2	D3	D4	D5	Overall		
Witte 2017	!	!	+	+	+	-	+	Low risk
Moussa 2021	+	+	+	+	+	+	!	Some concerns
							-	High risk

Summary of Findings

Summary of findings - Mirabegron compared with placebo for voiding disturbances				
Population: Patients with Parkinson's disease **Settings: Outpatient** **Intervention: Mirabegron, 50 mg daily, oral** **Comparison: Placebo**				
Outcomes	**Relative effect (mean difference [MD], 95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Day voids (number of voids, recorded in a 3-day voiding diary)	0.8 less voids per day in the Mirabegron group compared to Placebo (MD, -0.8; 95% CI, -3.04 to 1.43)	227 (3)	⊕⊕⊖⊖ **low**	**Reasons to downgrade:** -Inconsistency due to substantial heterogeneity -Imprecision due to low number of participants
Incontinence (number of episodes, recorded in a 3-day voiding diary)	1.03 less episodes per day in the Mirabegron group compared to Placebo (MD, -1.03; 95% CI, -2.14 to 0.09)	227 (3)	⊕⊕⊖⊖ **low**	**Reasons to downgrade:** -Inconsistency due to substantial heterogeneity -Imprecision due to low number of participants
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.				