

COMPARATIVE EFFICACY, SAFETY AND TOLERABILITY OF INTERVENTIONS FOR IDIOPATHIC DETRUSOR OVERACTIVITY AND OVERACTIVE BLADDER IN ADULTS: A COMPREHENSIVE SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Hypothesis / aims of study

The aim of this study was to compare the efficacy and safety of all conservative interventions for idiopathic detrusor overactivity (DO) and overactive bladder (OAB) in adults, using a comprehensive network meta-analytic framework.

Key interventions recommended for the management of OAB can be categorized into several broad classes including lifestyle interventions, physical therapies, behavioural therapies, drug therapies, and minor surgical management. However, it is known that long term compliance with drug therapy is low, and little is known about the comparative clinical effectiveness between the diverse range of interventions for OAB. To our knowledge, this is the first study to compare all conservative treatments for the management of idiopathic DO and OAB in a single coherent analysis of the most salient outcomes.

Study design, materials and methods

We searched Medline, EMBASE, and Cochrane systematic reviews up to January 5, 2016 for randomised controlled trials involving community dwelling adults with OAB symptoms, idiopathic DO, urge incontinence, and mixed incontinence where the predominant cause of incontinence was urgency. We excluded individuals with neurogenic disorders, pregnancy related incontinence, stress incontinence, benign prostatic hyperplasia, bladder outlet obstruction, lower urinary tract symptoms, and mentally impaired individuals, due to differences in aetiology. We included all interventions for the conservative management of OAB, excluding major surgical interventions such as augmentation cytoplasty and urinary diversion. Two reviewers independently assessed studies for eligibility. Disagreement was resolved by joint review and arbitration by a senior author if necessary. Internal validity was assessed through evaluation of random sequence generation, allocation concealment, blinding of outcome, blinding of participants, incomplete outcome data and selective reporting.

Primary outcomes included mean change from baseline in incontinence, urgency, voiding and nocturia episodes. Secondary outcomes were number of patients experiencing adverse events and discontinuations for adverse events or lack of efficacy. Random effects network meta-analysis was performed using class effects to account for similarities between different formulations of the same type of intervention.

Results

A total of 174 trials including 75,355 participants studying 140 interventions were analysed. Table 1 shows treatment effect estimates for the top five interventions relative to placebo for each of the primary outcomes. Sacral nerve stimulation was most effective for reducing urinary incontinence episodes (mean change: -8.47, 95% credible interval [CrI] -10.93, -5.77) and voiding episodes (-5.35, 95%CrI -9.43, -1.11). Electrostimulation plus vaginal oestrogen cream (1.25mg daily) was most effective for urgency episodes (-6.77, 95%CrI -8.3, -5.22). Estriol 1mg intravesically was most effective for nocturia (-2.19, 95%CrI: -3.15, -1.0). OnabotulinumtoxinA 200u gave mean reductions of -2.08 (95%CrI -2.87, -1.46)(incontinence), -2.28 (95%CrI -3.74, -1.29)(voiding) and -2.19 (95%CrI: -3.44,-1.05)(urgency episodes). Oxybutynin IR 5mg t.i.d and mirabegron ER 25mg q.d. did not feature in the top five interventions but comparatively had similar efficacy for incontinence episodes (-0.56 (95%CrI: -0.95,-0.24) versus -0.63 (95%CrI: -0.89,-0.41), and voiding episodes (-0.72 (95%CrI: -1.06,-0.36) versus -0.80 (95%CrI: -1.06,-0.54) respectively.

Table 2 shows the estimated odds ratios relative to placebo for the top five most hazardous interventions. Darifenacin ER 30mg (odds ratio [OR]: 6.31, 95%CrI 3.46, 11.46) had most patients experiencing adverse events. Solabegron IR 50mg (OR: 16.66, 95%CrI 2.11, 1239), had most discontinuations for adverse events. Serlopitant 4mg, a neurokinin 1 receptor antagonist, had the highest risk of patients discontinuing due to a lack of efficacy (OR:2.79, 95%CrI: 0.36, 57.68), though the 95% credible interval contained the point of no difference.

Interpretation of results

Sacral nerve stimulation was most effective for treating incontinence and voiding episodes. OnabotulinumtoxinA had the best overall efficacy and safety profile for treating OAB with incontinence. Electrostimulation was effective for treating OAB without incontinence. Mirabegron was equally effective to oxybutynin but with better tolerability.

Concluding message

This comprehensive systematic review and network meta-analysis has enabled all treatment modalities, of varying levels of invasiveness, for DO and OAB to be compared with one another in terms of efficacy, safety and tolerability. It is clear that sacral nerve stimulation dominates for certain outcomes, but the invasiveness and cost may make it less attractive as a primary intervention. Botulinum toxin appears to have significant advantages over other treatments and the new beta-3-adrenoreceptor agonists show comparable efficacy to established antimuscarinics but with improved tolerability.

Table 1: Table of results for top five interventions

Outcome	Rank	Treatment	Mean difference (95% CrI)
Incontinence	1	Sacral nerve stimulation	-8.47 (-10.93,-5.77)
	2	Electrostimulation + PFMT + BT	-2.16 (-3.13,-1.19)
	3	OnaBoNT-A 200U trigone sparing	-2.08 (-2.87,-1.46)
	4	Solifenacin/trospium + placebo injection	-2.02 (-2.99,-1.06)
	5	OnaBoNT-A 100U trigone sparing	-1.93 (-2.33,-1.52)
Voiding	1	Sacral nerve stimulation	-5.35 (-9.43,-1.11)
	2	Electrostimulation + PFMT + BT	-3.35 (-5.36,-1.24)
	3	OnaBoNT-A 200U trigone sparing	-2.28 (-3.74,-1.29)
	4	PFMT + BT	-2.16 (-3.96,-0.27)
	5	Tolerodine ER 4mg q.d + Neurostimulation	-1.93 (-2.72,-1.15)
Urgency	1	Electrostimulation + vaginal oestrogen cream 1.25mg/day	-6.77 (-8.3,-5.22)
	2	Electrostimulation	-4.67 (-5.7,-3.65)
	3	Vaginal oestrogen cream 1.25mg/day	-3.17 (-4.74,-1.61)
	4	Percutaneous tibial nerve stimulation	-2.68 (-4.55,-0.86)
	5	Cizolirtine citrate 400mg b.i.d	-2.35 (-4.33,-0.44)
Nocturia	1	Estriol 1mg intravesically	-2.19 (-3.15,-1)
	2	Estradiol 3mg intravaginally	-1.78 (-2.82,-0.67)
	3	Estradiol 1mg intravaginally	-0.54 (-1.11,-0.05)
	4	Tolterodine IR 2mg b.i.d + BT	-0.43 (-0.87,0.03)
	5	Electrostimulation + vaginal oestrogen cream 1.25mg/day	-0.47 (-0.81,-0.11)

Table 2: Table of results for five most hazardous/least tolerable interventions

Outcome	Rank	Treatment	Odds Ratio (95% CrI)
Occurrence of adverse events	1	Darifenacin ER 30mg q.d	6.31 (3.46,11.46)
	2	Imidafenacin 0.25mg b.i.d	4.62 (2.28,9.36)
	3	Tarafenacin 0.4mg q.d	3.42 (1.56,7.67)
	4	Solifenacin ER 20mg q.d	3.27 (1.56,7.37)
	5	Terodiline 25mg b.i.d	3.07 (1.14,8.73)
Discontinuation due to adverse events	1	Solabegron IR 50mg b.i.d	16.66 (2.11,1239)
	2	Imidafenacin 0.25mg b.i.d	11.37 (3.76,37.66)
	3	Solabegron IR 125mg b.i.d	11.46 (1.13,771.2)
	4	Trospium 30mg/day + Solifenacin 10mg/day (continuous)	8.67 (0.47,539.4)
	5	Cizolirtine citrate 400mg b.i.d	9.78 (2.87,63.96)
Discontinuation due to lack of efficacy	1	Serlopitant 4mg q.d	2.79 (0.36,57.68)
	2	ONO-8539 30mg b.i.d	2.32 (0.2,89.38)
	3	Serlopitant 1mg q.d	2.35 (0.29,49.45)
	4	Imidafenacin 0.1mg b.i.d	2.36 (0.59,9.05)
	5	Netupitant 100mg q.d	1.81 (0.15,29.54)

Disclosures

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Subjects: NONE