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Madhuvrata P[1], Singh M[2], Abdel-Fattah M[3]
1. *Sheffield Teaching Hospital,UK,* ***2.*** *Sheffield Teaching Hospital, UK,* ***3.*** *University of Aberdeen, UK*

WHICH ANTICHOLINERGIC DRUG FOR ADULTS WITH NEUROGENIC DETRUSOR OVERACTIVITY? A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED TRIALS

Hypothesis / aims of study
We aim to compare the efficacy, tolerability and safety of one anticholinergic drug versus another and also higher doses of anticholinergics versus lower dose in the treatment of adult neurogenic detrusor overactivity (NDO).

Study design, materials and methods :
Literature search of MEDLINE, EMBASE, Cochrane incontinence specialised trials register, clinicaltrials.gov and IUGA/ICS conference abstract databases was performed from 1966 to January 2011. Randomised trials (RTs) comparing one anticholinergic drug with other or two doses of the same anticholinergic drug, in adults with NDO were included. Trials comparing anticholinergics versus placebo were excluded. Data were extracted independently by two authors. Data was analysed using Rev-Man 5. The primary outcome was the clinical cure/ improvement; both patient-reported cure and objective cure. The secondary outcomes were quality of life (Qol), Overactive bladder symptoms (urinary frequency/24hrs, urgency/24hrs, incontinence/24hrs), Urodynamic outcomes (maximum cystometric capacity, maximum detrusor contraction, number of detrusor contractions, residual volume), adverse events (dry mouth) and withdrawals due to adverse events.

Fig1: Oxybutynin vs other AC- Change in frequency/24hrs and change in incontinence/24hrs

	Other drug			Oxybutynin				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
5.3.1 Change in frequency/24hr									
Fader 2007	-1.6	2	57	-1.2	1.8	57	38.2%	-0.40 [-1.10, 0.30]	
Gajewski 1986	-0.6	0.8	11	-1.3	0.8	15	43.2%	0.70 [0.08, 1.32]	
Stohrer 2007	-2.9	2.9	54	-2.5	3.3	52	18.6%	-0.40 [-1.58, 0.78]	
Subtotal (95% CI)			**122**			**124**	**100.0%**	**0.03 [-0.78, 0.84]**	
Heterogeneity: Tau² = 0.34; Chi² = 6.20, df = 2 (P = 0.04); I² = 68%									
Test for overall effect: Z = 0.07 (P = 0.95)									
5.3.2 Change in incontinence/24hrs									
Fader 2007	-0.9	1.7	57	-0.9	1.6	57	37.2%	0.00 [-0.61, 0.61]	
Gajewski 1986	-0.5	0.8	11	-1	0.8	15	36.3%	0.50 [-0.12, 1.12]	
Stohrer 2007	-1.6	2.3	54	-1.3	2	52	26.5%	-0.30 [-1.12, 0.52]	
Subtotal (95% CI)			**122**			**124**	**100.0%**	**0.11 [-0.33, 0.55]**	
Heterogeneity: Tau² = 0.03; Chi² = 2.59, df = 2 (P = 0.27); I² = 23%									
Test for overall effect: Z = 0.51 (P = 0.61)									

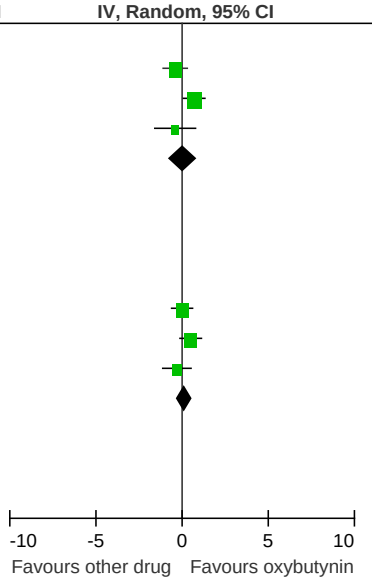
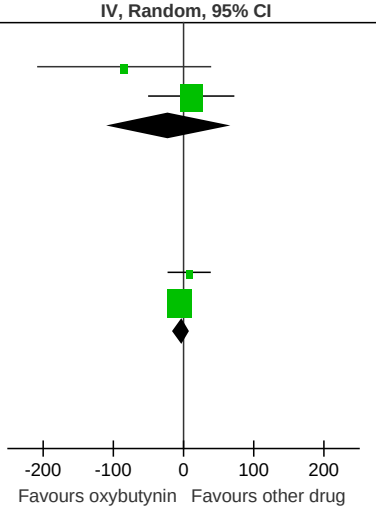


Fig 2: Oxybutynin versus other AC- Urodynamic parameters

	Other drug			Oxybutynin				Mean Difference	Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
5.2.1 Maximum cystometric capacity									
Gajewski 1986	198	129	6	282.5	117.9	12	19.4%	-84.50 [-207.40, 38.40]	
Stohrer 2007	309	166	46	298	125	45	80.6%	11.00 [-49.29, 71.29]	
Subtotal (95% CI)			**52**			**57**	**100.0%**	**-21.12 [-109.55, 67.31]**	
Heterogeneity: Tau² = 2121.06; Chi² = 1.87, df = 1 (P = 0.17); I² = 47%									
Test for overall effect: Z = 0.47 (P = 0.64)									
5.2.2 Maximum detrusor contraction									
Gajewski 1986	44.7	33	6	36.7	24	12	14.7%	8.00 [-21.69, 37.69]	
Stohrer 2007	38	31	46	43	29	45	85.3%	-5.00 [-17.33, 7.33]	
Subtotal (95% CI)			**52**			**57**	**100.0%**	**-3.09 [-14.48, 8.30]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%									
Test for overall effect: Z = 0.53 (P = 0.60)									



Results

11RTs with 767 men and womenincluded; 7 RTs comparing oral Oxybutynin to other anticholinergics, 2 RTs comparing different doses of same anticholinergic (trospium and tolterodine) and one trial comparing extended versus immediate release propiverine. A further trial compared methantheline, flavoxate and meladrazine, but reported no usable data for this meta-analysis.

- Oxybutynin versus other anticholinergic :7 RTs compared oxybutynin versus other anticholinergic drugs (propantheline, trospium, propiverine, intravesical atropine, intravesical oxybutynin and controlled release oxybutynin). Treatment duration ranged from 3 to 8 weeks. Meta-analyses showed better cure/improvement (Risk Ratio (RR) 0.80, 95% CI 0.52, 1.24) with oxybutynin when compared to other anticholinergics but not statistically significant. There was no difference in the mean change of frequency/24hr (Fig 1) (Weighted Mean Difference (WMD) 0.03, 95% CI -0.78, 0.84), mean change of incontinence/24hrs (WMD 0.11, 95% CI - 0.33, 0.55) (Fig 1), maximum cystometric capacity (Fig 2) (WMD -21.12, 95%CI -109.55, 67.31) and maximum detrusor contraction (WMD -3.09, 95% CI -14.48, 8.30) (Fig 2) at end of treatment between the groups. The dry mouth rate was higher in the oxybutynin group although not significant (RR 0.71, 95% CI 0.41, 1.21) and the withdrawals due to adverse events (RR 1.07, 95% CI 0.36, 3.17) were comparable. Only one study assessed Qol, but the data was not in usable form.
- Different doses of Tolterodine: Only one RT compared different doses of tolterodine (0.5mg vs 1mg vs 2mg vs 4mg) Outcomes were assessed at 2 weeks; the maximum cystometric capacity improved with increasing dose although not statistically significant. Dry mouth was reported to be increased with increasing dose of tolterodine but not significantly different between the different doses of tolterodine.
- Different dosing regimen of Trospium: One trial (Menarini 2006) reported different dosing regimens of trospium, comparing fixed dose (45mg/day) versus adjustable dose (permissible to increase dose to 90 or 135mg/day). Urodynamic outcomes were assessed: here was no significant difference in the change in maximum cystometric capacity (WMD -45.0, 95%CI -110.6, 20.6) or change in detrusor pressure (WMD 13, 95% CI -0.58, 26.6). There was no significant difference incompliance (WMD 8.0, 95% CI -34.41, 50.41) or incidence of dry mouth (RR 0.81, 95% CI 0.45, 1.46).
- Extended release versus immediate release Propiverine: One RT (Stohrer 2009) compared immediate release with extended release propiverine and the outcomes were assessed at 3 weeks. Data was not in usable form for this review. . Dry mouth was not different between the two groups.

Interpretation of results

This meta-analysis shows a trend towards higher cure /improvement rates however also higher rates of dry mouth with oxybutynin when compared to other anticholinergic drugs, both of which were not statistically significant. Similarly, there was no evidence of significant differences in urinary symptoms or urodynamic parameters at end of treatment between both groups. Only one RT comparing different doses of tolterodine, trospium chloride and extended versus immediate release propiverine were identified, therefore meta-analysis of these comparisons was not possible. This evidence is limited by heterogeneity of outcome measures, short-term follow up and relatively high risk of bias in some RTs. None of the RTs compared the newer antimuscarinic drugs such as Solifenacin, Fesoteridine, Darifenacin, and others.

Concluding message

In patients with NDO, there is no convincing evidence of better cure/ improvement in OAB symptoms with oxybutynin over other antimuscarinic drugs. High quality studies with longer follow-up incorporating standardised outcome measures and quality of life assessment are required. Efficacy and safety of newer anticholinergics should be evaluated in NDO.

Specify source of funding or grant	**None**
Is this a clinical trial?	**No**
What were the subjects in the study?	**NONE**