

ADVERSE EVENTS OF ANTICHOLINERGIC DRUGS FOR TREATING OVERACTIVE BLADDER SYMPTOMS IN ADULTS - A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMISED TRIALS.

Hypothesis / aims of study: We aim to compare the adverse events of different anticholinergic drugs for treatment of overactive bladder (OAB) symptoms in adults.

Study design, materials and methods

A literature search of MEDLINE, EMBASE, Cochrane incontinence specialised trials register, clinicaltrials.gov and IUGA/ICS conference abstract databases was performed in March 2011. Randomised trials (RTs) comparing one anticholinergic drug with other in adults with OAB or detrusor overactivity were included. Trials comparing one anticholinergic with placebo were excluded. Side-effect data was extracted independently by two authors. Data was analysed using Rev-Man 5. The side-effects assessed were dry mouth, constipation, blurred vision, voiding difficulty/urinary retention, fatigue/somnolence, insomnia/confusion/cognitive impairment, dizziness/vertigo/orthostatic disturbance and palpitations.

Results

47 RTs with 19251 men and women were included; Oxybutynin was compared with Tolterodine (14 RTs), Trospium (5 RTs), Propiverine (2 RTs), Propantheline (2 RTs), Darifenacin (2 RTs), Solifenacin (1 RT), Intravesical atropine (1 RT) and Emepronium (1 RT). Tolterodine was compared with Solifenacin (5 RTs), Propiverine (1 RT), Fesoterodine (3 RT), Trospium (1 RT) and Darifenacin (1 RT). Additional comparisons were Solifenacin vs Propiverine, Imedafenacin vs Propiverine and Solifenacin vs Darifenacin (1 RT each).

Dry mouth:

Oxybutynin versus other anticholinergic: Dry mouth was statistically significantly higher with Oxybutynin when compared to Tolterodine (RR 0.65 95% CI 0.60 to 0.71), Trospium (RR 0.64 95% CI 0.52 to 0.77), Propiverine (RR 0.77 95% CI 0.65 to 0.90) and Solifenacin (RR 0.43, 95% CI 0.30 to 0.60).

Tolterodine versus other anticholinergic: There was no difference when Tolterodine was compared to Solifenacin, Propiverine, Trospium and Darifenacin but a significantly higher number of patients experienced dry mouth with Fesoterodine than Tolterodine (RR 1.83 95% CI 1.61 to 2.08).

Propiverine versus other anticholinergic: Dry mouth rate was statistically significantly lower with Solifenacin and Imedafenacin when compared to Propiverine, but data were from 1RT only for each comparison.

Constipation:

Oxybutynin versus other anticholinergic: The constipation rate was statistically significantly higher with Trospium when compared to Oxybutynin (RR 2.73 95% CI 1.14 to 6.85). There was no statistically significant difference between Oxybutynin and Tolterodine, Propantheline, Propiverine and Solifenacin .

Tolterodine versus other anticholinergic: More patients taking Solifenacin (RR 2.78 95% CI 1.80 to 4.27) and Darifenacin reported constipation than those taking Tolterodine. There was no difference in the constipation rates when Tolterodine was compared to Fesoterodine .

Propiverine versus other anticholinergic: There was no significant difference in the constipation rates when Propiverine was compared to Solifenacin and Imedafeancin .

Blurred vision

Oxybutynin versus other anticholinergic: The blurred vision rate was higher with Oxybutynin when compared to Tolterodine (RR 0.42 95% CI 0.19 to 0.96), but lower with Oxybutynin when compared to Propiverine (RR 1.60 95% CI 1.08 to 2.37). There was no statistically significant difference between Oxybutynin and Propantheline or Trospium or Solifenacin.

Tolterodine versus other anticholinergic: There was no significant difference between Tolterodine and Solifenacin.

Propiverine versus other anticholinergic: There was no significant difference when Propiverine was compared to Solifenacin and Imedafeancin .

Voiding difficulty/urinary retention

Oxybutynin versus other anticholinergic: Significantly higher numbers of patients taking Oxybutynin reported voiding difficulty than those taking Tolterodine (RR 0.40 95% CI 0.24 to 0.65). There was no difference when Oxybutynin was compared to Propiverine and Trospium.

Tolterodine versus other anticholinergic: There was no difference when Tolterodine was compared to Solifenacin and Fesoterodine.

Propiverine versus other anticholinergic: There was no difference when Propiverine was compared to Solifenacin and Imedafenacin.

Fatigue/somnolence:

There was no statistically significant difference in the reported rates of fatigue/somnolence when Oxybutynin was compared to Tolterodine, Propantheline, Propiverine or Solifenacin. There was no difference when Tolterodine was compared to Solifenacin and but significantly lower fatigue/somnolence with Fesoterodine (RR 0.11 95%CI 0.01 to 0.83).

Insomnia/confusion/cognitive impairment

There was no statistically significant difference when Oxybutynin was compared to Tolterodine , Trospium or Propantheline.

Dizziness/vertigo/orthostatic disturbance

There was no statistically significant difference when Oxybutynin was compared to Tolterodine, Trospium, Propantheline, Propiverine or Solifenacin. There was no difference when Tolterodine was compared to Solifenacin and Fesoterodine.

Palpitation/tachycardia

There was no difference in palpitation when Oxybutynin was compared to Trospium and Tolterodine versus Solifenacin.

Interpretation of results

This meta-analysis shows statistically significantly higher risk of dry mouth, blurred vision and voiding difficulty in those taking Oxybutynin compared to Tolterodine. The dry mouth rate was higher with Oxybutynin when compared to all other anticholinergics, but there was no difference in any other adverse events. Those taking Tolterodine had significantly lower risk of constipation compared to Solifenacin and a lower risk of dry mouth compared to Fesoterodine. Fatigue/somnolence, however, was more commonly reported by those taking Tolterodine than with Fesoterodine. There was no other difference in the other adverse events assessed when Tolterodine was compared to other anticholinergics.

This evidence is limited by few studies in each comparison, short-term follow up and relatively high risk of bias in some RTs. A further limitation was that some studies made reference to important side effects (eg. Cardiac/CNS), but did not provide interpretable data as to their frequency and so could not allow comparison.

Concluding message: This meta-analysis will be helpful for anti-cholinergic selection based only on adverse events. Where the choice is between Oxybutynin and Tolterodine, Tolterodine may be preferred due to lower risk of dry mouth, blurred vision and voiding difficulty. Between Tolterodine and Solifenacin, Tolterodine may be preferred over Solifenacin due to lower risk of constipation. Between Tolterodine and Fesoterodine, Fesoterodine may be used in patients at risk of fatigue/somnolence, whereas Tolterodine may be preferred if less dry mouth is desirable. Dry mouth was the commonly reported outcome in all the studies. CNS, cardiac and visual symptoms were poorly reported. Studies in future should aim to assess and report all the adverse events associated with anticholinergic use, not just those occurring frequently. This is particularly relevant given a high proportion of OAB sufferers are elderly and at particular risk from side effects such as CNS and cardiac problems. Data could be collected using a uniform adverse events data collection sheet. This in turn would be useful to perform meta-analysis that could aid in counselling patients and selecting appropriate anticholinergics based on existing risk factors. High quality studies with longer follow-up and incorporating standardised adverse outcome measures are required.

Disclosures

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