



## Letter to the Editor

**Re: Giacomo Novara, Antonio Galfano, Silvia Secco, et al. A Systematic Review and Meta-Analysis of Randomized Controlled Trials with Antimuscarinic Drugs for Overactive Bladder. Eur Urol 2008;54:740–64**

Novara and co-workers have performed a Cochrane meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder (OAB) [1]. In lieu of the current EMMA approval of trospium chloride immediate release (IR; 20 mg, twice a day) and the scheduled licensing of trospium extended release (ER; 60 mg daily) within the European Union by 2009, this letter is intended to request inclusion of both the trospium IR and ER data. Trospium ER 60 mg is licensed by the US Food and Drug Administration (FDA) and sold in the United States under the brand name Sanctura XR.

The authors have used active-controlled trials as a study-inclusion goal; however, please note that not all of the included trials have met this criterion (eg, reference 34 in Novara et al [1]). An additional consideration is that the Novara meta-analysis used a Cochrane methodology, which requires numerical averages, or means, for comparison. We have followed this approach and included percent mean reduction from baseline; however, we have also included medians. We believe the inclusion of median values is appropriate, given that some efficacy data within Novara et al's Table 1 are, in fact, medians (eg, reference 33 regarding fesoterodine for urge urinary incontinence [UUI] and references 28–31 regarding darifenacin). The inclusion of both means and medians will permit an accurate comparison of the results.

Regarding trospium ER 60 mg once daily, two parallel randomized-placebo controlled trials including 1165 patients with OAB have been performed and reported [2,3]. The OAB disease severity of the enrolled patients was average UUI per day of 4.1, diurnal TV of 10.7, and nocturnal TV of 2.4,

which indicate a severe state of disease when compared with the trials included in the meta-analysis. From the trospium ER trials, statistically significant reductions in UUIs and TV were identified at day 5 of initiating therapy and maintained throughout the 12-wk double-blinded study period, including median reduction of UUI (–80% trospium ER vs –55% placebo;  $p < 0.0001$ ) and mean reduction of frequency (–20.5% trospium ER vs –14.0% placebo;  $p < 0.0001$ ). Of the 1165 patients enrolled, 89% placebo and 88% trospium ER completed the 12-wk randomized-placebo controlled trial. Adverse events (AEs) leading to withdrawal were reported in 3.2% of placebo and 5.2% of trospium ER patients. The most common AEs were dry mouth (10.7% trospium ER vs 3.7% placebo) and constipation (8.5% trospium ER vs 1.5% placebo). These rates compare favorably with the AE results for trospium IR reported in the meta-analysis (Novara et al's Table 9 [1]) and provide proof of design of the trospium ER formulation.

Regarding trospium IR 20 mg twice a day, one randomized-placebo controlled trial including 512 patients with OAB was performed and reported [4]. The OAB disease severity of the enrolled patients was average UUI per day of 4.1, diurnal TV of 10.8, and nocturnal TV of 2.1, which again illustrate the severity of the OAB disease. From this trial, statistically significant reductions in UUIs and TV were identified at day 1 of initiating therapy and maintained throughout the 12-wk double-blinded study period, including mean reduction of UUI (–59% trospium IR vs –44% placebo;  $p < 0.0001$ ) and mean reduction of frequency (–19% trospium IR vs –10% placebo;  $p < 0.0001$ ). Of the 512 patients enrolled, an identical rate of study completion (83.6%) was reported in placebo and trospium IR trial arms. AEs were reported in 5.7% of placebo and 8.8% of trospium IR patients. The most common AEs were dry mouth (21.8% trospium IR vs 6.5% placebo) and constipation (9.5% trospium IR vs 3.8% placebo).

**Table 1 – Tabulated calculations of both the pooled trospium extended release (ER) trials [5] and the trospium immediate release (IR) trial [4]**

Trial	Treatment		No. patients randomized	Duration, wk	Disease	% prior therapy	Mean UUI/day
Staskin et al [5]	Trospium ER 60 mg vs placebo		1165	12	OAB	53.4	4.14
Zinner et al [4]	Trospium IR 20 mg vs placebo		512	12	OAB (UUI)	54.0	4.1
	Mean change in daytime micturitions per 24 h	Mean change in nighttime micturitions per 24 h	Mean change in micturitions per 24 h	Mean change in volume voided per micturition (ml)	Mean change in urgency episodes per 24 h	Mean change in UUI episodes per 24 h	Mean change in 24-h “Dry rate” from baseline
Trospium ER, 60 mg [5]	–1.94 (–18%)	–0.84 (–36%)	–2.7 (–21%)	31 (21%)	–1.5 (–29%)	–2.4 (–59%; –80% median)	35%
Trospium IR, 20 mg [4]	–1.9 (18%)	–0.47 (22%)	–2.4 (19%)	32 (21%)	–2.3 (20%)	–2.3 (59%; –79% median)	21%
	AE rate	Withdrawals due to AE	Dry mouth	Constipation	AUR	Vision abnormality	Headache
Trospium ER, 60 mg [5]	27.2%	5.2%	10.7%	8.5%	1%	<1%	1.4%
Trospium IR, 20 mg [4]	44%	8.8%	21.8%	9.5%	<1%	<1%	6.5%

AE = adverse event; AUR = acute urinary retention; UUI = urge urinary incontinence.

Tabulated calculations of both the pooled trospium ER trials [5] and the trospium IR trial [4] are included Table 1 in the Cochrane meta-analysis format.

**Conflicts of interest:** Michael G. Oefelein is an employee of Allergan; Allergan markets Sanctura XR. David Staskin consults and speaks for Allergan regarding the Sanctura XR brand.

## References

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