

Pharmacotherapy in Overactive Bladder—State of the Art

a report by

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Overactive bladder (OAB) is a syndrome with multiple symptoms including urinary urgency, with or without urge incontinence and usually with increased frequency of micturition and nocturia, which is not explained by metabolic or local pathologic factors. The prevalence in the US is 33 mio (million) – 12 mio ‘wet’. Overall, 16.6% of the population aged ≥ 40 years have the symptoms of OAB and the prevalence of OAB increases with age. The OAB definition – provided by the international continence society (ICS) in 2002 – emphasises the symptomatic nature of the syndrome. The aetiology of OAB may be neurogenic, myogenic or both. Despite the high prevalence, a significant number of patients remain untreated. The economic burden of OAB was estimated at US\$12.6 billion in the US in 2000.

Therapeutic Interventions in OAB

In terms of therapy different options are available: behavioural therapy, containment, pharmacotherapy or invasive treatment. This report focuses on the pharmacological treatment strategies¹.

Antimuscarinic agents such as oxybutynin, tolterodine, trospium, propiverine, solifenacin and darifenacin are used widely in addition to imipramine and oestrogen. The efficacy of such agents is classically thought to be mediated through the blockade of muscarinic receptors in the detrusor muscle and the urothelium. M3 receptors are the primary mediators in the bladder. Compared with placebo, antimuscarinics significantly improved urge urinary incontinence and urgency episodes. The most common adverse effects (AEs) to an anticholinergic are dry mouth, constipation and blurred vision. Antimuscarinic agents have the potential to cause significant depressant effects to the central nervous system (CNS), such as memory impairment and sleep disruption. The extent to which an OAB medication has CNS effects is determined by the extent to which the agent crosses the blood-brain

barrier. Oxybutynin immediate-release (IR) and extended-release (ER) were significantly more effective than placebo in reducing incontinence episodes. Oxybutynin ER was superior to tolterodine IR in terms of efficacy and comparable in terms of tolerability. Tolterodine significantly improved urge urinary incontinence and urgency episodes. Dry mouth was the most common AE in all studies, more frequent with tolterodine than placebo and more frequent with IR than ER formulations. Discontinuations due to AEs were similar between tolterodine (ER and IR) and placebo, and lower than using oxybutynin. Trospium significantly reduced the number of urge incontinence episodes and urgency voids compared with placebo. The most common AEs seen were dry mouth and constipation. Discontinuations due to AEs were also higher with trospium than placebo. Propiverine was numerically less effective than oxybutynin IR and tolterodine IR in changing cystometric bladder capacity. Propiverine was more effective than tolterodine IR at increasing volume per void and in reducing incontinence episodes. Propiverine IR appeared similar in terms of the incidence of overall AEs in comparison with oxybutynin IR, but resulted in less severe dry mouth. Propiverine and tolterodine IR were comparable in terms of tolerability. Solifenacin (5mg and 10mg) was significantly superior to placebo in reducing the multiple symptoms of OAB. No dose response was seen in the reduction of urge incontinence episodes. Discontinuations due to AEs were similar between solifenacin (5mg and 10mg) and placebo. Darifenacin showed a high affinity and selectivity for M3 receptors over other muscarinic subtypes and there were no adverse effects on fertility. Darifenacin 7.5mg or 15mg once daily showed significant improvement in all OAB symptoms versus placebo. Darifenacin was well tolerated, dry mouth and constipation rarely led to discontinuation due to the low potential to cross the blood-brain barrier. Darifenacin has a favourable CNS and cardiovascular safety profile,

1. Chapple, C et al., “The effects of antimuscarinic treatments in overactive bladder: a systematic review and meta-analysis”, *European Urology* 48 (2005); pp. 5–26.

CNS and cardiovascular adverse events were comparable to placebo.

Oxybutynin transdermal²⁻³ system is a novel approach in the treatment of OAB: the patch is applied on the abdomen, hip or buttock on a clean, dry and smooth area. It is effective, with a comparable efficacy to tolterodine ER and oxybutynin IR, in both treating naïve and treatment-experienced patients. Significant improvement in quality-of-life parameters could be demonstrated. Dry mouth is on placebo level. There is a very low incidence of constipation, blurred vision and dizziness. Concerning the skin reactions 93% patients reported no erythema and 83.9% patients reported no pruritus. Many undesirable effects (mainly CNS, cardiac and gastrointestinal (GI)) known to be associated with oral anticholinergics were not observed with oxybutynin transdermal. Age, bodyweight, gender, race, tobacco and concurrent illness did not influence the outcome.⁴ Over 90% were satisfied with the patch appearance and did not find it bothersome, dry mouth was reported on placebo level and there was a low incidence of

anticholinergic side effects. The patch was easy to use, with a high patient satisfaction. Sixty-seven per cent of patients indicated they would prefer to use a patch for future OAB treatment.

Should antimuscarinics fail, the following options still exist:

- topical pharmacological treatment;
- vanilloids: Capsaicin I Resiniferotoxin (RTX);
- electromotive drug administration (EMDA);
- intravesical botox;
- permanent neurostimulation; and
- bladder augmentation in urinary diversion

Conclusions

OAB significantly impairs patient quality of life and antimuscarinics are the preferred method of redressing this. In order to avoid gastrointestinal AEs, oxybutynin transdermal system offers an excellent alternative with equal efficacy and probably reduced side-effects. Should the systemic drug therapy fail, topical options should be exhausted prior to moving to invasive therapy. ■

2. Dmochowski, R, "Improving the tolerability of anticholinergic agents in the treatment of overactive bladder", *Drug Safety* (2005);28:7: pp. 583–600.
3. Dmochowski, R et al., "Transdermal oxybutynin in the treatment of adults with overactive bladder: combined results of two randomized clinical trials", *World J Urol*. DOI 10.1007/s00345-005-0012-8 (2005).
4. Luber, K, Dmochowski, R, "Some side-effect profiles and PK in the elderly up to 52 weeks as the overall population", poster presented at AGS (2003).