

## PATIENT-SELECTED GOALS IN OVERACTIVE BLADDER: A PLACEBO CONTROLLED RANDOMISED DOUBLE-BLIND TRIAL OF TRANSDERMAL OXYBUTYNYN FOR THE TREATMENT OF URGENCY AND URGE INCONTINENCE.

### Hypothesis / aims of study

Randomised controlled trials have provided Level 1 evidence of efficacy for a range of anticholinergics for overactive bladder (OAB) [1]. However they may overestimate the benefits of anticholinergics in clinical practice, firstly because they typically selectively recruit and randomise patients with severe disease, and secondly because they employ outcome measures that are of limited relevance to patients. The primary aim of this placebo controlled randomised trial of transdermal oxybutynin 3.9mg/day was to compare achievement of patient-selected goals [2] with conventional bladder diary and quality of life outcomes, in a population of adult women with OAB, representative of the range of severities seen in clinical practice.

### Study design, materials and methods

Double-blind, randomised, 2-arm parallel group study over 4 weeks, with 2 week placebo run-in period, and optional 8 week open-label extension (results not included here). Adult women with  $\geq 3$  month history of OAB symptoms, with or without urge incontinence, were recruited from a tertiary referral urogynaecology unit. Participants completed 3-day bladder diaries, recording frequency and nocturia, and incorporating both the validated Patients Perception of Intensity of Urgency Scale to assess urgency and urge incontinence episodes. Quality of life was assessed using the ICIQ-LUTSqol, previously known as the King's Health Questionnaire. Participants recorded up to 5 goals for treatment at baseline, and subsequently scored achievement of these goals on a visual analogue scale [2]. Study numbers were assigned based on order of recruitment. Each study number was previously randomly allocated to either active transdermal oxybutynin 3.9mg/day or matching placebo, with medication packs made up off site. A sample size of 74 was estimated to provide an 80% power to detect a 30% difference between active and placebo treatments for the primary outcome of goal achievement, with alpha set at 0.05. Anticipating a 20% loss to follow up, 96 patients were randomised. Between groups differences were compared with the Mann-Whitney U test, t-test, and Fisher's exact test. Within groups differences were compared with the Wilcoxon signed rank test. Analyses were performed using SPSS version 16.0.

### Results

98 women were recruited, with 96 randomised. Mean age was 51.5 (range 21-86). Mean BMI was 27.5 (range 17.6-39.8). Mean parity was 2.0 (range 0-6). 69 (70.4%) were Caucasian. 66 (68.8%) were anticholinergic naïve. At baseline mean recorded bladder diary parameters for all participants were 8.0 voids/day, 1.4 voids/night, 1.0 urge incontinence episodes/day, and 3.6 urgency episodes/day. On baseline diaries approximately one third of patients had no leakage (OABdry). There were no significant baseline differences in diary variables between placebo and active groups ( $p$  all  $>0.05$ ).

Transdermal oxybutynin, in comparison to placebo, was associated with small, but significant improvements in frequency (-0.71 voids/day vs. +0.13 voids/day,  $p=0.01$ ), urge incontinence (-0.64 leakage episodes/day vs. -0.20 leakage episodes/day,  $p=0.04$ ), and urgency episodes (-1.27 episodes/day vs. -0.28 episodes/day,  $p=0.01$ ). There was no significant effect on nocturia (-0.10 voids/night vs. +0.04 voids/night,  $p=0.66$ ) (Figure 1). There was no significant difference observed between mean goal achievement in the transdermal oxybutynin group and placebo group (41.9% vs. 33.4%,  $p=0.209$  t-test) (Figure 2). There was a small but significant correlation between mean goal achievement and change in total ICIQ-LUTSqol score ( $\rho=0.252$   $p=0.038$ ), implying the validity of goal achievement as an outcome measure in OAB.

Both placebo and active groups made significant improvements from baseline in the Incontinence Impact, Role Limitations, Physical Limitations, and Emotions domains of the ICIQ-LUTSqol (all  $p<0.05$ ). However, there were no statistically significant differences between active and placebo groups for 8 of 9 domains (Role Limitations domain  $p=0.021$ , otherwise  $p>0.05$ ). Analysis of domain by domain minimally important clinical differences (MID) [3] for the ICIQ-LUTSqol showed between 17.2% and 48.3% of participants achieving these MIDs, but again with no statistically significant difference between groups ( $p>0.05$  all domains).

The safety analysis includes all participants who received at least one dose of study medication ( $n=95$ ). 39 (41.1%) patients experienced at least one adverse event, of which 35 were classified as mild, and 4 as moderate (2 in each group). 7 (7.4%) patients withdrew from the study during run-in or double blind treatment due to adverse events. 18 (38.2%) patients in the active group experienced either erythema or pruritus, with 7 (14.9%) experiencing at least one systemic adverse event, of which the commonest was dry mouth. 13 (27.1%) patients in the placebo group experienced either erythema or pruritus, with 6 (12.5%) experiencing at least one systemic adverse event

### Interpretation of results

In comparison to participants enrolled in Phase 3 trials for transdermal oxybutynin, these participants had milder OAB at baseline. The improvements in bladder diary parameters were smaller than previously reported, and overall of limited clinical significance. As a direct consequence patient-selected goal achievement was low for both active and placebo groups, with no difference between groups. Quality of life improvements were also limited, with only a minority of patients achieving the MIDs for the ICIQ-LUTSqol. The rate of systemic adverse events, and discontinuations due to adverse events, was similar to that reported in Phase 3 trials. However the rate of mild skin reactions was substantially higher, and this difference is probably due to closer monitoring of adverse events. These findings, in particular the failure to achieve patient-selected goals, may explain the disparity between excellent results observed with anticholinergics, including transdermal oxybutynin, in many existing randomised controlled trials, compared with the poor persistence, and patient disillusionment that is common in clinical practice.

### Concluding message

In women with OAB, over a 4 week period, in comparison to placebo, transdermal oxybutynin 3.9mg/day leads to small but significant improvements in frequency, urgency, and urge incontinence, but no significant difference in achievement of patients' own goals for therapy, and limited impact on quality of life.

### References

1. Cochrane Database Syst Rev (2006) ; 4 , CD003781
2. Int Urogynecol J Pelvic Floor Dysfunct (2008) 19(1) ; 81-4.
3. BJOG (2004) 111 ; 605-12

Figure 1: Change in bladder diary variables from baseline to 4 weeks

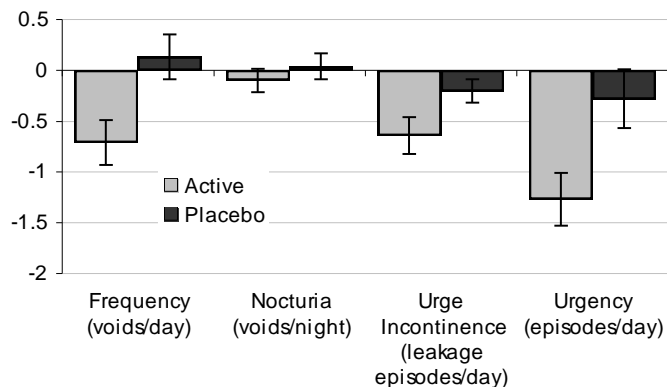
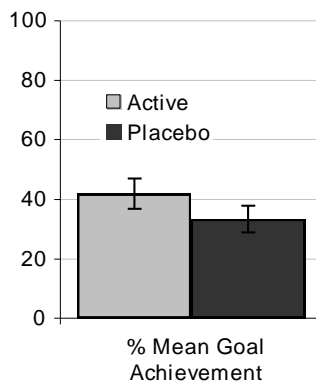


Figure 2: Mean goal achievement at 4 weeks



<b>Specify source of funding or grant</b>	<b>Unrestricted educational grant from UCB Pharma</b>
<b>Is this a clinical trial?</b>	<b>Yes</b>
<b>Is this study registered in a public clinical trials registry?</b>	<b>Yes</b>
<b>Specify Name of Public Registry, Registration Number</b>	<b>International Standard Randomised Controlled Trial Number Register, ISRCTN87161129</b>
<b>What were the subjects in the study?</b>	<b>HUMAN</b>
<b>Was this study approved by an ethics committee?</b>	<b>Yes</b>
<b>Specify Name of Ethics Committee</b>	<b>King's College Hospital Research Ethics Committee</b>
<b>Was the Declaration of Helsinki followed?</b>	<b>Yes</b>
<b>Was informed consent obtained from the patients?</b>	<b>Yes</b>