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Transdermal Oxybutynin

Claudine M. Baldwin and *Gillian M. Keating*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Contents

Abstract

▲ Oxybutynin inhibits contraction of the detrusor muscle in the overactive bladder by binding to muscarinic M_3 receptors and blocking acetylcholinergic activation.

▲ The transdermal oxybutynin system, applied twice weekly, delivers continuous oxybutynin over a 96-hour patch wear period. The transdermal route of administration avoids the extensive first-pass metabolism of oxybutynin to its active metabolite, *N*-desethyloxybutynin.

▲ In two well designed trials in patients with overactive bladder, transdermal oxybutynin 3.9 mg/day decreased the number of incontinence episodes and increased average voided volume to a significantly greater extent than placebo. Urinary frequency was improved to a significantly greater extent with transdermal oxybutynin than with placebo in one trial but not the other.

▲ There was no significant difference between transdermal oxybutynin and extended-release oral tolterodine for any of these endpoints.

▲ Health-related quality-of-life improvements with transdermal oxybutynin were shown in patients with overactive bladder in the open-label MATRIX trial, as demonstrated by significant improvements in all domains of the King's Health Questionnaire.

▲ Transdermal oxybutynin is generally well tolerated in patients with overactive bladder. The majority of patients who discontinued transdermal oxybutynin treatment in two pivotal trials did so because of application-site reactions. However, none discontinued treatment because of dry mouth.

Features and properties of transdermal oxybutynin (Oxytrol®, Kentera®)	
Indication	
Overactive bladder	
Mechanism of action	
Anticholinergic (antimuscarinic) and spasmolytic activity	
Dosage and administration	
Route of administration	Transdermal
Dosage	3.9 mg/day
Application frequency	Twice weekly (every 3–4 days)
Pharmacokinetic profile of oxybutynin after single 39 cm^2 patch application (delivering 3.9 mg/day) in healthy volunteers	
Mean peak plasma concentration	3.4–4.0 ng/mL (oxybutynin) 5.0–5.8 ng/mL (*N*-desethyloxybutynin)
Median time to peak plasma concentration	36–48 h (oxybutynin) 48 h (*N*-desethyloxybutynin)
Mean area under the plasma concentration-time curve	284–324 ng • h/mL (oxybutynin) 435–504 ng • h/mL (*N*-desethyloxybutynin)
Adverse events	
Most common events	Application-site reactions, dry mouth, constipation, nausea, vision disturbance, dysuria and somnolence

The International Continence Society defines overactive bladder as 'urgency, with or without urge urinary incontinence, usually with frequency and nocturia', where urgency describes a sudden and compelling desire to urinate that is difficult to delay.[1] Urgency incontinence is considered to be a result of detrusor overactivity.[2] The overactive bladder symptom complex is estimated to affect between 16% and 17% of the worldwide population, with incontinence occurring in approximately one-third of these persons.[1] Overactive bladder can be an extremely bothersome condition that can cause marked health-related quality-of-life (HR-QOL) disruption and is often unreported and undiagnosed, despite being a condition that can be effectively managed. Options for the management of overactive bladder include surgical, behavioural and pharmacological approaches, where the first choice should be the least invasive treatment with the smallest potential for adverse events that is appropriate for the individual.[3]

Anticholinergic agents are the primary choice of pharmacological intervention for the management of overactive bladder.[3] Oxybutynin is an anticholinergic agent with well established efficacy in the treatment of overactive bladder, having been in clinical use in oral form for nearly 30 years.[4] It is generally accepted that many of the anticholinergic adverse events associated with oral oxybutynin result from the active metabolite, *N*-desethyloxybutynin, peak plasma concentrations of which are higher than those of the parent drug due to extensive first-pass metabolism.[5] A transdermal formulation of oxybutynin (Oxytrol®, Kentera®) has been developed with the aim of avoiding hepatic metabolism, thereby reducing the incidence of anticholinergic adverse events.[6] Of these events, dry mouth is a major reason for which patients decide to discontinue otherwise successful anticholinergic therapy for overactive bladder.[7] The oxybutynin transdermal system is a three-layered, matrix-type patch composed of a backing film, an adhesive/drug layer and a release liner.[8] In the EU, transdermal oxybutynin is approved for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency in patients with overactive bladder.[9] It is also available for use in this indication in the US.[8]

The oral[10,11] and transdermal[12] formulations of oxybutynin have been previously reviewed in *Drugs & Aging*; this article provides an overview of the efficacy and tolerability of transdermal oxybutynin, and its effects on HR-QOL in patients with overactive bladder.

Medical literature on the use of transdermal oxybutynin in patients with overactive bladder was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

The pharmacodynamic properties of oxybutynin have been reviewed previously[10-12] and are summarized briefly in this section.

- Oxybutynin is a tertiary amine ester with mixed anticholinergic and spasmolytic activity, and some local anaesthetic effects.[13] Oxybutynin is a racemic mixture of R- and S-isomers; its antimuscarinic activity resides mainly in the R-isomer.[8] The therapeutic benefits of oxybutynin in the treatment of overactive bladder are conferred through binding to muscarinic M_3 receptors in the detrusor muscle of the bladder, preventing acetylcholinergic activation and thereby relaxing the muscle.[9]
- In radioligand binding studies, muscarinic receptor binding affinity values (pK_i) were 8.2 for oxybutynin and 8.2 for *N*-desethyloxybutynin (vs 9.5 for atropine) in isolated human bladder, and 8.5 and 8.7 (vs 9.4 for atropine) in isolated human parotid gland.[13] The muscarinic receptor affinities of oxybutynin did not significantly differ between bladder and parotid gland tissues, but did significantly ($p < 0.05$) differ for *N*-desethyloxybutynin.[13]
- In functional experiments, oxybutynin and *N*-desethyloxybutynin competitively antagonised carbachol-induced contractions of isolated human detrusor muscle, with equilibrium dissociation constant (pA_2) values of 7.8 and 7.6.[13] Oxybutynin dose-dependently inhibited electrical stimulation-

induced detrusor muscle contractions, with maximal inhibition (87% for oxybutynin and 91% for *N*-desethyloxybutynin) achieved at drug concentrations of 10 μmol/L.[13]

- The advantages of transdermal oxybutynin over oral oxybutynin were demonstrated in an *in vivo* study in rats. Following administration via transdermal patch, oxybutynin bound to bladder muscarinic receptors without the long-lasting binding to exocrine receptors and inhibitory effects on cholinergic salivation seen with orally administered oxybutynin.[14]

- Oxybutynin binding to muscarinic receptors was slow and reversible, with dissociation constant (K_d) values (12 hours post-dose) of 337 pmol/L in the bladder, 699 pmol/L in the submaxillary gland, 369 pmol/L in the heart and 305 pmol/L in the colon.[14]

- In cystometric studies in patients with overactive bladder, transdermal oxybutynin significantly increased both volume to first detrusor contraction and maximum urinary bladder capacity.[15] Patients with overactive bladder treated for 6 weeks with either transdermal (n = 33) or oral (n = 30) oxybutynin had increases in average bladder volume at first detrusor contraction of 66 mL ($p < 0.01$ vs baseline) and increases in average maximum cystometric capacity of 53 mL ($p = 0.001$ vs baseline), whereas increases with oral oxybutynin (45 and 51 mL) were not significant. Increases in post-void residual volume of 13 and 16 mL with transdermal and oral oxybutynin did not differ significantly from washout average volumes of 41 and 25 mL.[15]

2. Pharmacokinetic Profile

The pharmacokinetic profile of oxybutynin for the immediate-[10] and extended-release[11] oral formulations and the transdermal formulation[12] have been reviewed previously. The pharmacokinetics of transdermal oxybutynin are overviewed in this section.

Absorption and Distribution

- Oxybutynin is slowly absorbed (via passive diffusion) from the transdermal system following patch application to intact skin.[12] *In vitro* skin flux studies showed that both enantiomers of oxybutynin are absorbed equally across human epidermis.[16]

- The oxybutynin transdermal system provides continuous delivery of oxybutynin over 96 hours.[17] The drug is detectable in the plasma after a lag time of approximately 2 hours following patch application. Thereafter, plasma oxybutynin concentrations rise gradually over 24–36 hours, remain relatively stable for ≈24 hours, then decline slightly over the remainder of the 96-hour wear period.[17] Steady-state is achieved during the second patch application period.[9]

- After a single application of a 39 cm^2 patch (delivering oxybutynin 3.9 mg/day) to the buttock, hip or abdomen of healthy adult volunteers, mean maximum plasma oxybutynin concentrations (C_{max}) were 3.4–4.0 ng/mL over the three application sites; plasma *N*-desethyloxybutynin concentrations were approximately 1.5 times higher (5.0–5.8 ng/mL).[17] The median time to C_{max} (t_{max}) was 36–48 hours for oxybutynin and 48 hours for *N*-desethyloxybutynin).

- The mean area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC_∞) for oxybutynin was 324, 311 and 284 ng • h/mL after buttock, hip and abdominal patch application, respectively. The corresponding AUC_∞ values for *N*-desethyloxybutynin were 504, 488 and 435 ng • h/mL.[17]

- Oxybutynin absorption with patch application to the buttock was bioequivalent to application to the abdomen or the hip in that the 90% confidence intervals (CIs) of the C_{max} and AUC_∞ ratios for oxybutynin and *N*-desethyloxybutynin at these sites were within standard bioequivalence limits (90% CI 0.80, 1.25).[17]

- Bioequivalence was also established between the back and buttocks in a further study (available as a poster) in 45 healthy volunteers.[18] Although 90% CIs of the C_{max} ratio for these sites for oxybutynin (1.21) [CI 1.11, 1.31] were slightly outside the limit

of strict bioequivalence (80–125%), the 90% CIs of the AUC from 0 to 96 hours (AUC_{96}) ratios for the parent drug and the C_{max} and AUC_{96} ratios for *N*-desethyloxybutynin were within bioequivalence limits.[18]

- In a multiple-dose trial in 26 healthy volunteers, C_{max} and AUC values increased dose-proportionally according to patch surface area (13, 26 and 39 cm^2).[16] Median t_{max} values for oxybutynin and *N*-desethyloxybutynin were 10 and 24 hours for all three patch sizes.[16]
- Mean plasma oxybutynin concentrations were less variable during transdermal administration (3.9 mg/day) than after extended-release oral administration (10 mg/day) in healthy volunteers.[19] Mean oxybutynin C_{max} and AUC_{24} values did not significantly differ between the two formulations. However, the fluctuation index was 0.7 for transdermal oxybutynin compared with 1.3 for extended-release oral oxybutynin.[19]
- Systemic exposure to *N*-desethyloxybutynin was significantly reduced with transdermal oxybutynin compared with the extended-release formulation, evidenced by the difference in *N*-desethyloxybutynin : oxybutynin AUC ratios (1.2 vs 4.1; $p < 0.001$).[19]
- Oxybutynin is widely distributed into body tissues once systemically absorbed.[8] The parent drug and the active metabolite are extensively protein-bound (≈85%). Following a 5 mg intravenous dose of oxybutynin, the estimated volume of distribution of oxybutynin was 193 L.[8]

Metabolism and Elimination

- Oxybutynin is primarily metabolized by the cytochrome P450 (CYP) enzymes (predominantly CYP3A4, which is mostly found in the gut wall and in the liver, and in small amounts in the skin).[8] Metabolites other than *N*-desethyloxybutynin include the phenylcyclohexylglycolic acid, which is inactive.[8]
- Transdermal administration of oxybutynin substantially bypasses the extensive presystemic first-pass metabolism that occurs with oral administration, reducing the formation of *N*-desethyloxybutynin[8] (and thus reducing systemic exposure to the active metabolite and the incidence of anticholinergic adverse events [section 4]).
- Oxybutynin and *N*-desethyloxybutynin are eliminated with an apparent half-life ($t_{1/2}$) of ≈7–8 hours following removal of the transdermal patch.[8] Less than 0.1% of the administered dose is excreted in the urine as unchanged drug and ≤0.1% is excreted as *N*-desethyloxybutynin.[8]
- There are no significant alterations in the pharmacokinetic profile of transdermal oxybutynin according to age, sex or race (although the metabolism of oxybutynin appears to be lower in Japanese volunteers than in Caucasian volunteers). There is no experience with the use of transdermal oxybutynin in paediatric patients, nor in patients with hepatic or renal impairment.[8]
- There have been no specific drug interaction studies performed with transdermal oxybutynin. However, like other anticholinergic drugs, oxybutynin may potentially alter the absorption of concomitant medications due to effects on gastrointestinal motility.[8] In addition, CYP enzymes play an important role in the biotransformation of many drugs, therefore, concomitant administration of drugs sharing this metabolic pathway may result in relevant drug interactions.[9]

3. Therapeutic Efficacy

The efficacy of transdermal oxybutynin in the treatment of overactive bladder has been evaluated in several well designed clinical trials[15,20,21] and in a large community-based study,[22] which will be discussed in this section, with a particular focus on the approved transdermal oxybutynin dosage (39 cm^2 patch delivering a nominal dosage of 3.9 mg/day).

Where specified, statistical analyses of primary efficacy results from the reviewed trials were performed using the intent-to-treat (ITT)[20] or modified ITT (mITT)[21,22] population, using last observation carried forward imputation.[20-22]

Comparison with Immediate-Release Oral Oxybutynin

A 6-week, randomized, double-blind, multicentre study compared the efficacies of transdermal oxybutynin and immediate-release oral oxybutynin in 76 patients with overactive bladder who had demonstrated symptom improvement following ≥6 weeks of oral oxybutynin treatment.[15] Patients who had three or fewer incontinence episodes per day and a ≥30% increase in episodes following a 2-week washout from previous immediate-release oral oxybutynin therapy were randomized to receive transdermal oxybutynin (applied twice weekly) or immediate-release oral oxybutynin administered twice or three times daily), in a double-dummy manner, for 6 weeks. The oxybutynin dosage was titrated according to anticholinergic symptoms.[15] Subjects with overflow incontinence secondary to outlet obstruction or noncontractile/underactive detrusor, and medical conditions or therapies that may cause or contribute to urinary incontinence, were excluded.[15]

- Six weeks of transdermal oxybutynin or immediate-release oral oxybutynin treatment significantly decreased the average daily number of incontinence episodes (based on a 3-day patient urinary diary) [primary endpoint] in adults with urge urinary incontinence.[15] Both formulations significantly ($p < 0.0001$) decreased the average daily number of incontinence episodes from 7.2 in both treatment groups at the end of the 2-week washout period to 2.4 and 2.6 at 6 weeks.[15]
- Transdermal oxybutynin and immediate-release oral oxybutynin both significantly ($p < 0.0001$) improved urinary leakage (as assessed by a patient-completed visual analogue scale [VAS] for efficacy) from the end of the washout period to the 6-week endpoint. VAS score changes in the two respective treatment groups were 5.8 and 6.0.[15]
- Transdermal oxybutynin, but not immediate-release oral oxybutynin, significantly increased both maximum urinary bladder capacity and the volume to first detrusor contraction in this trial [section 1].[15]

Comparisons with Placebo and Extended-Release Tolterodine

The efficacy of transdermal oxybutynin has been evaluated in two 12-week, randomized, double-blind, placebo-controlled, multicentre trials in patients with overactive bladder, or urge or mixed urinary incontinence.[20,21]

Participants ($n = 512$ [mITT][21] and 361 [ITT][20]) were predominantly female (92%[21] and 93%[20]), were aged ≥18 years (mean age 61.4[21] and 63.5[20] years) and had a diagnosis of overactive bladder with either pure urge or predominantly urge episodes. Patients were required to have previously responded to pharmacological treatment for overactive bladder in one trial,[20] while the other included both previously-treated (≈22%) and treatment-naive patients.[21] Participants were asked to maintain a consistent fluid intake and to continue with their non-pharmacological methods of overactive bladder management.[20,21]

Patients with incontinence considered related to chronic illness, anatomical abnormalities/weaknesses or concomitant medications were excluded from one of the double-blind trials.[21] In the other trial, patients who had undergone lower urinary tract surgery in the previous 6 months, who had overflow urinary incontinence, or diagnoses of interstitial cystitis, urethral syndrome or painful bladder syndrome were excluded.[20]

Outcome measures (not distinguished as primary or secondary in one of the trials)[20] included (i) the change from baseline in the number of daily[20] or weekly (specified primary endpoint)[21] incontinence episodes (based on 3-[20] or 7-day[21] urinary diaries, both of which have been shown to provide accurate and reproducible data on the clinical manifestations of overactive bladder);[23] (ii) the change from baseline in the average daily urinary frequency;[20,21] (iii) the change from baseline in average urinary volume per void[20,21] (both prespecified as secondary endpoints in one trial);[21] and (iv) the proportions of patients achieving complete continence (defined as no diary-recorded incontinence episodes at study end).[20]

In one of the double-blind trials, patients were randomized to receive transdermal oxybutynin 1.3, 2.6 or 3.9 mg/day, or placebo,[21] while in the other, patients were randomized to treatment with transdermal oxybutynin 3.9 mg/day, extended-release oral tolterodine 4 mg once daily or placebo.[20] Transdermal patches were changed twice per week in both of the studies.

- Twice-weekly transdermal oxybutynin improved urinary incontinence in patients with overactive bladder, as demonstrated by significant decreases in the number of incontinence episodes per week[21] or per day[20] in two pivotal trials.
- Transdermal oxybutynin 3.9 mg/day decreased the number of weekly incontinence episodes from baseline to a significantly greater extent than placebo (median change of −19.0 vs −14.5 episodes per week; $p = 0.017$) in one trial.[21] In the other trial, transdermal oxybutynin 3.9 mg/day and tolterodine decreased the number of daily incontinence episodes to a significantly greater extent (from 4.7 to 1.9 and 5.0 to 1.9) than placebo (from 5.0 to 2.9) [median change of −2.9 and −3.2 vs −2.1 episodes per day; both $p < 0.02$ vs placebo].[20]
- Urinary frequency was decreased with transdermal oxybutynin 3.9 mg/day.[21] In one trial, the mean number of urinations per day decreased to a significantly greater extent with oxybutynin 3.9 mg/day (from 11.8 to 9.5) than with placebo (from 12.4 to 10.7) [mean change −2.3 vs −1.7 micturitions per day; $p = 0.0457$].[21]
- Reductions in urinary frequency with transdermal oxybutynin did not differ from those with placebo in the other trial (mean decrease of 1.9 vs 1.4 micturitions/day).[20] In contrast, such decreases with tolterodine were significant versus placebo (mean decrease of 2.2. vs 1.4 micturitions/day; $p = 0.0025$). There was no significant difference between the two active treatment groups for this endpoint.[20]
- Transdermal oxybutynin 3.9 mg/day improved average voided volume.[20,21] Mean voided volume increased to a significantly ($p < 0.05$) greater extent with oxybutynin 3.9 mg/day (from 170 to 202 mL) than with placebo (from 175 to 188 mL) [median change 24 vs 6 mL; $p = 0.0063$] in one trial.[21]
- In addition, average voided volume increased to a significantly ($p < 0.05$) greater extent with oxybutynin 3.9 mg/day or tolterodine than with placebo (median 24 and 29 vs 5.5 mL, respectively, and mean 32 and 29 vs 9 mL, respectively), with no significant difference between the active treatment groups.[20] Median (mean) baseline values were 160 mL (165 mL), 150 mL (165 mL) and 171 mL (175 mL) in oxybutynin, tolterodine and placebo recipients, respectively.[20]
- According to last diary entries in one trial, significantly more transdermal oxybutynin recipients (39%) and tolterodine recipients (38%) than placebo recipients (22%) recorded having achieved complete continence at endpoint (both $p = 0.014$ vs placebo).[20]
- The effects of transdermal oxybutynin and extended-release oral tolterodine on the daily number of incontinence episodes, micturition frequency and average void volume did not significantly differ.[20]

The Matrix Trial

The effects of transdermal oxybutynin on HR-QOL were evaluated in an open-label, multicentre, community-based study (mITT population of 2593 patients) known as the MATRIX (Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin) trial.[22] The primary HR-QOL results of the MATRIX trial have been fully published,[22] as have some secondary analyses,[24-26] while others are available as abstracts only.[27-33]

The MATRIX trial was a 'real-life' study that employed broad entry criteria to obtain a clinically representative patient population.[25] Patients received open-label treatment with transdermal oxybutynin 3.9 mg/day for up to 6 months. Centres participating in the MATRIX trial were randomized to provide patients with either standard instructions for the use of transdermal oxybutynin or standard instructions plus additional educational materials pertaining to overactive bladder (e.g. information on behavioural modification).[22]

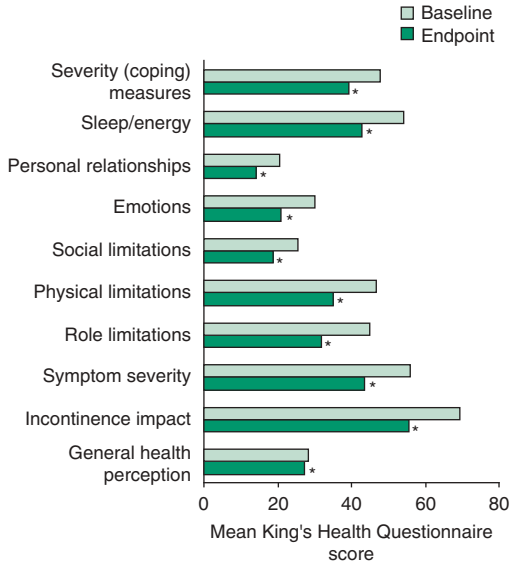

Fig. 1. Effects of transdermal oxybutynin on health-related quality of life in patients with overactive bladder. Mean King's Health Questionnaire scores at baseline (n = 2592) and endpoint (n = 2336) in patients treated with transdermal oxybutynin 3.9 mg/day for up to 6 months in the open-label multicentre MATRIX trial.[22] * $p \leq 0.001$ vs baseline.

The primary outcome measure in the MATRIX trial was the change from baseline at study end in HR-QOL, assessed using the King's Health Questionnaire (KHQ), a validated, 27-item tool that assesses ten domains of HR-QOL (General Health Perception, Incontinence Impact, Symptom Severity, Role Limitations, Physical Limitations, Social Limitations, Emotions, Personal Relationships, Sleep and Energy, and Severity [coping] Measures).[22] Changes from baseline of ≥3 points for the General Health Perception and Symptom Severity domains and ≥5 points for all other domains were considered clinically meaningful.[22] Other outcome measures in the MATRIX trial included changes from baseline in depression (measured using the Beck Depression Inventory [BDI]-II),[28] work productivity (measured using the Work Productivity Questionnaire [WPQ], which assesses four domains of work [physical, time management, mental and output demands, scored from 0 to 100 [best to worst]) [26] and participant satisfaction,[33] as well as differential treatment outcomes in various patient subpopulations.[24,25,29,30]

- Transdermal oxybutynin 3.9 mg/day for up to 6 months significantly improved HR-QOL in community-based patients with overactive bladder in the MATRIX trial.[22] All KHQ domains were significantly improved from baseline at study end ($p \leq 0.001$; figure 1). Furthermore, improvements were clinically meaningful for all but one domain (General Health Perception).[22] Prior treatment history for overactive bladder had no impact on HR-QOL improvements.[29]

- Transdermal oxybutynin recipients reported significant improvements in depressive symptoms and the impact of overactive bladder on sexual activity and relationships.[28] At baseline, 32.2% of patients were classed as depressed (BDI-II scores >12), significantly decreasing to 23.2% by study end ($p < 0.001$).[28] More than 20% of patients showed improvements in several depressive symptoms, including fatigue, concentration difficulties, alteration in sleep patterns, loss of energy and loss of interest in sexual activity.[28] The latter improved significantly with transdermal oxybutynin treatment ($p < 0.0001$ vs baseline).[24] Coital incontinence decreased with treatment (reported by 22.8% of patients at baseline vs 19.3% at study end).

- Furthermore, 19.1% of patients reported that the effects of overactive bladder on sexual activity had improved (11.2% reported worsening) [$p < 0.001$] and 19.6% of patients reported that the effects of overactive bladder on their relationships with partners had improved (11.9% reported worsening) [$p < 0.001$] after transdermal oxybutynin treatment.[24]

- Transdermal oxybutynin also significantly improved work productivity in the MATRIX trial.[26] Approximately 39% of the MATRIX study population (1112 participants) were in full- or part-time employment at the start of the trial. After transdermal oxybutynin treatment, WPQ time scale scores improved from 39.7 at baseline to 28.2 at study end, with corresponding changes from 27.1 to 22.4 for the physical scale, 28.0 to 18.2 for the

mental scale and 23.2 to 14.6 for the output scale (all $p < 0.001$).[26]

- WPQ summary scores were also significantly improved from baseline, with the mean index score reducing from 8.2 to 5.5 at study end, and the work productivity loss score reducing from 7.7% at baseline to 5.2% (both $p < 0.0001$).[26]
- In terms of other symptoms associated with overactive bladder, nocturia severity and nocturnal enuresis improved in 41% and 17% of patients over the duration of the trial, and each worsened in 10% of participants (both $p < 0.001$).[27]
- When MATRIX results were analysed according to sex and other subgroups, transdermal oxybutynin treatment effects were similar in men with or without prostate disease,[25] and in women treated or not treated with concomitant noncontraceptive estrogen therapy.[32] Subgroup analyses according to patient age (patients aged <75 or ≥75 years[31] and women aged <45 or ≥45 years[30]) showed no significant differences in terms of HR-QOL improvements with transdermal oxybutynin treatment for overactive bladder.[30,31]
- In an analysis of patient satisfaction during the MATRIX trial, overall satisfaction (patients reporting being 'satisfied' or 'very satisfied' with treatment in response to monthly telephone interviews) at 1, 3 and 6 months was 68.7%, 69.4% and 73.1%, with similar satisfaction levels reported for ease of application, effectiveness and tolerability at these timepoints.[33] Perceived severity of overactive bladder significantly ($p < 0.001$ vs baseline) decreased during the study, with an observed correlation with treatment satisfaction.

4. Tolerability

The data presented in this section were obtained from the randomized, comparative trials[15,20,21] and the longer-term, open-label, MATRIX trial[22] discussed in section 3. Additional data have been obtained from the pooled results[34] of two of the double-blind trials[20,21] (which included only patients treated with transdermal oxybutynin 3.9 mg/day or placebo).

- Transdermal oxybutynin was a generally well tolerated treatment for overactive bladder. Application-site reaction was the most common adverse event reported in clinical trials.[15,21,22]
- Approximately 7% and 16% of patients treated with transdermal oxybutynin in the two double-blind trials experienced application-site erythema and application-site pruritus. Of these, event severity was mild to moderate in 71% and 95% of patients, and resulted in treatment discontinuation in 3.7% and 3.3% of patients.[34] In general, application-site reactions with transdermal oxybutynin increased with increasing patch strength and occurred with the greatest incidence during the first 12 weeks of treatment.[6]
- The most common systemic anticholinergic adverse events reported in placebo-controlled trials included dry mouth, constipation, nausea, vision disturbance, dysuria and somnolence (figure 2). There was no significant difference between transdermal oxybutynin and placebo in terms of the incidence of these events.[34]
- According to pooled safety data,[34] 100 of 242 (41.3%) transdermal oxybutynin recipients and 61 of 245 (24.9%) placebo recipients reported adverse

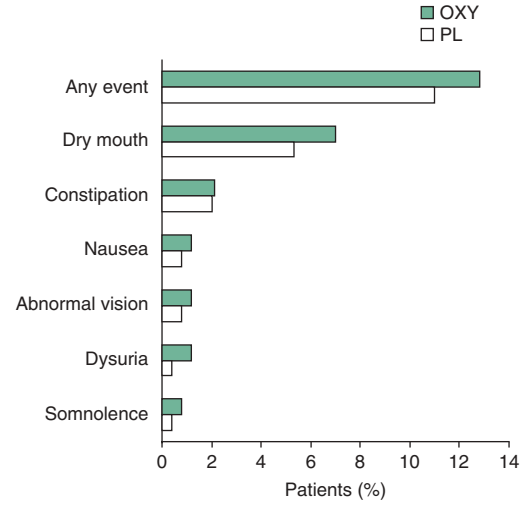

Fig. 2. Tolerability of transdermal oxybutynin (OXY) in patients with overactive bladder. Most commonly reported systemic anticholinergic adverse events occurring in numerically more OXY 3.9 mg/day (n = 242) than placebo (PL; n = 245) recipients. Pooled results[34] from two 12-week, randomized, double-blind, multicentre trials.[20,21]

events considered by the investigators to be related to treatment. Most events were mild to moderate in severity, although 27 (11.2%) and 3 (1.2%) patients in each treatment group discontinued because of adverse events. Among transdermal oxybutynin recipients, the majority of patients who discontinued treatment did so because of application-site reactions; notably, no patients discontinued transdermal oxybutynin treatment because of dry mouth.[34]

- In the trial comparing transdermal oxybutynin with extended-release oral tolterodine, anticholinergic events were the most commonly reported treatment-related adverse events (13% of patients). Dry mouth was reported in 4.1% of transdermal oxybutynin recipients in this study (no significant difference vs placebo).[20] However, dry mouth occurred in significantly more tolterodine (7.3%) than placebo (1.7%) recipients ($p < 0.05$).[20]
- Dry mouth occurred in significantly less transdermal oxybutynin recipients than immediate-release oral oxybutynin recipients in one 6-week trial (38% vs 94%; $p < 0.001$).[15] A total of 67% of transdermal oxybutynin recipients and 33% of immediate-release oral oxybutynin recipients reported a reduction in the severity of dry mouth compared with prior oral oxybutynin treatment.[15]
- Transdermal oxybutynin was well tolerated in a community-based population treated for up to 6 months in the MATRIX study.[22] Drug-related anticholinergic events such as dry mouth, constipation and dizziness were reported in 2.6%, 1.5% and 0.7% of patients, respectively. Drug-related application-site reactions (pruritus, erythema, dermatitis and irritation) were reported in 14% of participants.[22]

5. Pharmacoeconomic Considerations

This section summarizes pharmacoeconomic data pertaining to transdermal oxybutynin.

A US pharmacoeconomic evaluation used a decision-analysis model to compare the cost effectiveness of eight antimuscarinic treatment options for overactive bladder (transdermal oxybutynin 3.9 mg/day, extended-release oral oxybutynin 10 mg/day and tolterodine 4 mg/day, immediate-release oral oxybutynin 15 mg/day and tolterodine 4 mg/day, darifenacin 15 mg/day, solifenacin 5 mg/day and trospium chloride 40 mg/day).[35] The model had a 3-month time frame and was constructed from the payer's perspective. Clinical outcomes, drug costs, and costs for adverse events and the treatment of overactive bladder-associated co-morbidities were included in the model. Cost data and probabilities of treatment success were obtained from the literature. A Swedish cost-minimization analysis from the societal perspective included direct medical costs relating to transdermal oxybutynin or oral tolterodine treatment, as well as the cost of treating the six most frequently observed adverse events in the comparative trial (constipation, diarrhoea, dry mouth, and application-site erythema, pruritus and rash).

Pharmacoeconomic analyses of transdermal oxybutynin, in common with all pharmacoeconomic analyses, are subject to a number of limitations. Pharmacoeconomic analyses based on clinical trials extrapolate the results of such trials to the general population; however, patient populations, rates of compliance and major outcomes in clinical trials may differ from those observed in real-life practice. Modelled analyses, such as those presented in this section, rely on a number of assumptions and use data from a variety of sources. Results of pharmacoeconomic analyses may not be applicable to other geographical regions because of differences in healthcare systems, medical practice and unit costs.

- The expected 3-month costs per patient treated with transdermal oxybutynin was $US3603, with costs for other agents ranging from $US3373 for solifenacin to $US3769 for immediate-release oral oxybutynin (2005 costs). Cost-effectiveness ratios ranged from $US6863 (solifenacin) to $US21 685 (immediate-release oral oxybutynin); transdermal oxybutynin (with a ratio of $US10 346) was dominated only by solifenacin. One-way sensitivity analyses confirmed the robustness of these results over the specified range of discontinuation rates and unit costs for the comparators, and the costs of treating overactive bladder-induced co-morbidities. However, the model was sensitive to the success rate of each treatment.[35]

- Transdermal oxybutynin 3.9 mg/day appeared to be cost saving compared with extended-release oral tolterodine 4 mg/day in the treatment of patients with urge or mixed urinary incontinence, according to a cost-minimization analysis (available as an abstract plus poster)[36] based on a 12-week comparative trial discussed in section 3.[20]
- The total cost of 12 weeks of treatment was SEK1067 per patient for transdermal oxybutynin and SEK1113 per patient for tolterodine (2007 costs). The cost of treating adverse events was regarded as an insignificant proportion of total treatment costs for both alternatives due to the low frequency of events that required treatment and the low costs of treatment for those individual events. Sensitivity analyses confirmed the robustness of these results.[36]

6. Dosage and Administration

The recommended dosage of transdermal oxybutynin for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency is one patch (39 cm^2; nominal dosage 3.9 mg/day) applied twice weekly.[8,9]

The patch should be applied to clean, dry and healthy skin, on the hip, abdomen or buttock, then replaced after 3–4 days. Oxybutynin is released from the acrylic adhesive matrix of the transdermal system continuously over the 3- to 4-day wear duration.[8] A new application site should be used with each new patch and reapplication to the same site avoided for ≥7 days.[8,9]

Local prescribing information should be consulted for more detailed information, including contraindications, warnings and precautions.

7. Transdermal Oxybutynin: Current Status

Transdermal oxybutynin is approved for use in the EU,[9] the US[8] and other countries worldwide for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency in patients with overactive bladder. Twice-weekly transdermal oxybutynin is an effective treatment for overactive bladder in adults, as demonstrated in several clinical trials. Compared with oral oxybutynin, the transdermal formulation has tolerability advantages, which include a reduced propensity to cause anticholinergic adverse events such as dry mouth. While the patch may be associated with local application-site reactions in some patients, transdermal oxybutynin has been shown, in the 6-month, community-based MATRIX study, to improve HR-QOL.

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Correspondence: *Claudine M. Baldwin*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz