REVIEW ARTICLE

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Improving the Tolerability of Anticholinergic Agents in the Treatment of Overactive Bladder

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Abstract

Pharmacological treatment for overactive bladder has centred around the interruption of the detrusor activity that is central to urge and incontinence symptoms. The majority of patients with this disorder are treated with antimuscarinic agents. These drugs have been demonstrated to improve urgency, frequency of micturition and urge incontinence, all of which are primary symptoms of overactive bladder; however, they are also commonly associated with anticholinergic adverse effects, most notably dry mouth. Attempts to increase tolerability have included the development of advanced formulations that regulate release of the active ingredient and the development of pharmacological agents that target the desired bladder receptors more specifically and accurately. Although all agents provide good efficacy, tolerability is greatly affected by the formulation used to deliver the active pharmacological agent, as well as the specificity of the

targeted receptors. Clinical trials involving a transdermal formulation of oxybutynin have shown that this delivery method may be associated with a lower incidence of anticholinergic adverse events compared with both the immediate-release and the extended-release oral formulations of traditional agents, as well as the most recently approved agents – trospium chloride, solifenacin and darifenacin. Much is still being learned about the function and specificity of muscarinic receptors, which will support the development of agents with sustained efficacy and enhanced tolerability compared with the available formulations to date. These include the S-isomer of oxybutynin, as well as selective muscarinic M_2 receptor antagonists.

Overactive bladder is a condition characterised by urinary urgency that may or may not be accompanied by involuntary loss of urine (urge incontinence) and is usually associated with eight or more micturitions per day (frequency) and waking at night to void one or more times (nocturia).[1,2] Although widely under-reported, in large part because of the embarrassment associated with urinary problems,[3-5] overactive bladder is estimated to affect 33 million adults in the US, with roughly one-third of these adults experiencing incontinence episodes.[1,6] The symptoms of overactive bladder have a great impact on quality of life, often resulting in psychological distress, limitation of daily activities, embarrassment, anxiety, feelings of a loss of control and depression.[7-10] Overactive bladder is a significant cause of dependency as well as nursing home placement among older adults.[11] Although patients have adopted various coping mechanisms to avoid having embarrassing incontinence episodes occur in public, the physiological abnormalities underlying bladder instability are reasonably well understood and effective treatments for overactive bladder are available.

1. Physiological Factors Contributing to Overactive Bladder Symptoms

Several key physiological components are involved in micturition. Bladder filling and voiding are primarily controlled via an alternating process of parasympathetic and sympathetic nervous stimulation of the detrusor and bladder neck muscles.[12] During bladder filling (sympathetic relaxation), the detrusor muscle is relaxed, while the bladder neck is toned and contracted. During micturition (parasympathetic contraction), the detrusor is contracted and the bladder neck is relaxed. Noradrenaline (norepinephrine) and its activation of β-adrenergic receptors is responsible for sympathetic relaxation and subsequent bladder filling, while acetylcholine activates muscarinic receptors, producing contraction and resultant voiding. In patients with overactive bladder, bladder filling, during which the detrusor muscle should be relaxed, is interrupted by frequent idiopathic detrusor contractions.

Muscarinic receptors within the bladder are primarily located on the detrusor muscle, within the epithelial lining of the inner bladder surface and on the parasympathetic and sympathetic nerve endings.[12] Five types of muscarinic receptors have been identified: M_1, M_2, M_3, M_4 and M_5.[12,13] In human detrusor tissue, the primary subtypes present are M_2, which are located on the urothelium and detrusor cells, and M_3, which are mainly located on the detrusor smooth muscle; the former outnumbering the latter by 3 to 1.[14,15] Despite this fact, it is primarily the M_3 receptors that mediate the contraction of bladder musculature, mainly by stimulating hydrolysis of phosphoinositide, which leads to a release of intracellular calcium in the detrusor (figure 1).[14,16-19] M_3 receptors are also located on the parotid gland and in the gastrointestinal tract.[16,17] Recent results from animal experiments have shown that M_2 receptor-mediated contractions also occur via inhibition of cyclic adenosine monophosphate (cAMP)-mediated relaxation of bladder smooth muscle.[14] Therefore, bladder emptying has been shown to occur via dual mechanisms: M_3 receptor-mediated direct contraction and M_2 receptor-mediated reversal of bladder relaxation. This dual mechanism may result in more complete emptying of the bladder during micturition (figure 1).[20]

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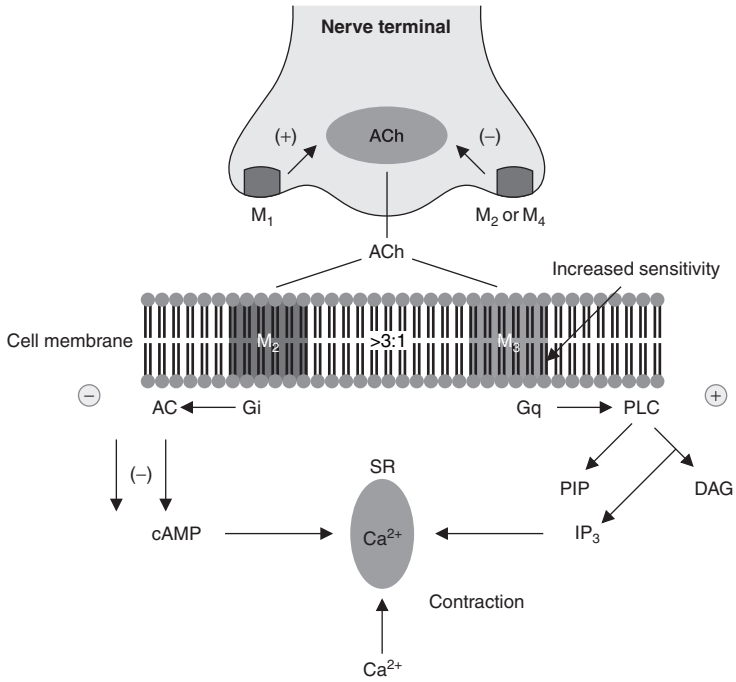

Fig. 1. Muscarinic receptors (M_1–M_4) at the post-ganglionic parasympathetic nerve terminal in overactive bladder. **AC** = adenylyl cyclase; **ACh** = acetylcholine; **Ca^{2+}** = calcium; **cAMP** = cyclic adenosine monophosphate; **DAG** = diacylglycerol; **Gi** = subclass of G protein (inhibitory); **Gq** = subclass of G protein; **IP_3** = inositol-1,4,5-trisphosphate; **PIP** = phosphatidylinositol-4,5-bisphosphate; **PLC** = phospholipase C; **SR** = sarcoplasmic reticulum.

2. Available Treatment Options

The treatment of overactive bladder requires therapy that is individualised to each patient's lifestyle and cognitive ability.[1] Realistic goals should be discussed with each patient prior to the initiation of therapy. Treatment options include nonpharmacological therapy, pharmacotherapy and surgery.

Because it is the least invasive approach to treatment, nonpharmacological therapy is often recommended as a first-line option for the management of overactive bladder symptoms. These therapies work by teaching patients new skills or habits and include pelvic floor muscle (Kegel) exercises with or without biofeedback, pelvic floor electrical stimulation (PFES), modification of fluid intake and diet, timed voiding and prompted voiding. Pelvic floor muscle exercises are designed to strengthen the muscles of the pelvic floor, thereby improving urethral sphincter function.[21] Because many patients have problems identifying these particular muscles, biofeedback may be used to instruct patients on how to perform these contractions correctly. A form of passive exercise, PFES improves urethral closure by activating pudendal nerve afferents, which in turn activate pudendal and hypogastric nerve efferents, causing contraction of periurethral muscles.[22] Unfortunately, pelvic floor muscle exercises (both Kegels and PFES) require a moderate level of cognitive functioning and, therefore, may not be effective in some older patients. For patients with cognitive dysfunction, scheduled toileting or prompted voiding may be helpful.[23] Prompted voiding is helpful in decreasing accidents in patients with dementia. It involves training the healthcare professional to prompt the patient to urinate. Additionally, timed voiding, also known as habit training, involves setting a schedule for urination based on the patient's habits. It has been demonstrated that the use of behavioural and pharmacological treatment in conjunction provides better outcomes (reduction in urge incontinence episodes) than either treatment

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alone.[24] Often, pharmacological options are preferred because they require minimal effort on the part of the patient to be effective.

A variety of treatments have been used to treat overactive bladder. However, only the antimuscarinic agents oxybutynin, tolterodine, trospium chloride, solifenacin and darifenacin have been approved for this indication. While the latter three drugs have only recently been approved, oxybutynin and tolterodine have demonstrated indisputable efficacy in the reduction of overactive bladder symptoms in many randomised, placebo-controlled, double-blind clinical trials and in various patient populations.[25-29] Unfortunately, patients often discontinue using oral formulations because of high levels of anticholinergic adverse events.[30] This issue has prompted research and advances in the development of new formulations and new antimuscarinic agents aimed at improving tolerability.

3. Overview of the Pharmacology of Antimuscarinic Agents

3.1 Non-selective Antimuscarinic Agents

Antimuscarinic agents achieve their clinical effect by binding to muscarinic receptors, thereby blocking the activity of acetylcholine and resulting in reduced contraction of the detrusor muscle. However, these agents also antagonise muscarinic receptors in tissues other than the bladder, such as the parotid gland and the gastrointestinal tract.[18,19] Results from a preclinical study involving guinea pigs indicate that oxybutynin and tolterodine appear to bind to muscarinic receptors in bladder tissue with similar affinity; however, oxybutynin binds to the parotid gland with approximately 8-fold greater affinity than does tolterodine.[31] *In vivo* studies using anesthetised cats also demonstrated that tolterodine has a greater inhibitory effect on bladder contraction than on salivation.[31,32] Trospium chloride, a new quarternary ammonium antimuscarinic agent, has been shown to have the least selectivity and highest overall affinity of the muscarinic receptor subtypes.[33] Solifenacin, another new, non-selective antimuscarinic agent that binds to M_1, M_2 and M_3 receptors,[34] has demonstrated a higher affinity for antimuscarinic receptors in the bladder than for the salivary gland (similar to tolterodine).[35] Animal studies have suggested that it has the highest degree of bladder selectivity *in vitro* and *in vivo* compared with tolterodine and oxybutynin.[36,37]

3.2 Selective Antimuscarinic Agents

Darifenacin is the first M_3-selective antimuscarinic agent approved by the US FDA for the treatment of overactive bladder.[34] In addition, laboratory evidence suggests that darifenacin is more highly selective for the bladder than for the salivary gland.[38] The efficacy and tolerability of all of these agents has been reviewed in randomised controlled clinical trials showing that formulation and receptor activation play a viable role in tolerability.

4. Clinical Efficacy and Tolerability of Immediate-Release (IR) Antimuscarinics

4.1 Oxybutynin IR

In early placebo-controlled studies, the oral immediate-release (IR) formulation of oxybutynin demonstrated efficacy in reducing symptoms of overactive bladder, such as urinary urgency and urge incontinence.[29,39] In a randomised, double-blind trial involving 30 patients with idiopathic urge incontinence, the efficacy and safety of oxybutynin IR (5mg three times daily) was compared with that of placebo.[39] Patients were treated first with one treatment option for 20 days and then with the second 20-day treatment following a 10-day washout period. Compared with placebo, oxybutynin was associated with a significant decrease in total micturition frequency (4.5 vs 5.7 times per day, $p < 0.01$) and urgency (9 vs 13 episodes, $p < 0.01$). Both oxybutynin and placebo demonstrated statistically significant improvements in pathological micturition frequency; this symptom declining from ten to one ($p < 0.001$) in the oxybutynin group and from ten to four ($p < 0.02$) in the placebo group. Most importantly, patients treated with oxybutynin experienced a significant reduction in urge incontinence episodes (a decline from 21 to 9, $p < 0.001$), although these also decreased in the placebo group (from 21 to 15, $p < 0.005$). Notwithstanding, oxybutynin was significantly more effective than placebo in reducing urge incontinence episodes. These re-

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Table I. Pharmacokinetic parameters of antimuscarinic agents in healthy individuals at steady state[a,b]

Antimuscarinic agent	Regimen	Mean t_{max} (h)	Mean C_{max} (ng/mL)	Mean AUC_{ss} (ng•h/mL)	Mean $t_{1/2}$ (h)	References
Oxybutynin IR	5mg tid	0.5 (1.5)	12.4 (4.1)	81 (43)	2.0 (0.9)	41,48
Oxybutynin ER	15mg od	5.2 (3.7)	6.7 (2.1)	109 (43)	13.8 (2.9)	48
Oxybutynin TDS[c]	3.9mg daily, applied every 3–4d	10[d]	6.6 (2.4)	408 (108)	7–8 (following removal)	49
Tolterodine IR[e]	2mg bid	1.2 (0.5)	2.6 (2.8)	6.7–7.8	2.2 (0.4)	50
Tolterodine ER[e]	4.0mg od	4 (2–6)[f]	3.4 (4.9)	6.7–7.8	6.9 (3.5)	51

a All values for both oxybutynin and tolterodine refer to parent compound, not metabolite.

b Values in parentheses are standard deviations unless otherwise noted.

c Following application to the abdomen.

d t_{max} given as median.

e Results are for extensive metabolisers.

f Range.

AUC_{ss} = area under the concentration-time curve at steady state; **bid** = twice daily; **C_{max}** = maximum serum concentration; **ER** = extended release; **IR** = immediate release; **od** = once daily; **TDS** = transdermal delivery system; **tid** = three times daily; **t_{max}** = time of occurrence of C_{max}; **$t_{½}$** = terminal elimination half-life.

sults correlated with significant improvements in objective signs, such as time of first desire to void (improved in 14 patients receiving oxybutynin vs 13 receiving placebo, $p < 0.025$), volume at which there was a very strong desire to void (improved in 15 patients receiving oxybutynin vs 11 receiving placebo, $p < 0.01$) and detrusor pressure when there was a strong desire to void (normal or reduced in 13 patients receiving oxybutynin vs 8 receiving placebo; $p < 0.02$). Although efficacious, oxybutynin was associated with a high incidence of anticholinergic adverse events in this study. The most common adverse events were dry mouth (73% for oxybutynin vs 27% for placebo), vision trouble (33% vs 17%) and nausea (33% vs 13%).

In another double-blind, crossover, placebo-controlled study, postmenopausal women diagnosed with idiopathic detrusor instability (n = 37) were treated with both oral oxybutynin (5mg four times daily) and placebo, with 2-week treatment periods for each and a 2-week washout period between treatments.[29] A combination of visual analogue symptom scoring and urodynamic testing was utilised at baseline and after each treatment period to determine efficacy. Symptoms measured with the visual analogue scale included urge incontinence, urinary urgency, stress incontinence and enuresis. Patients treated with oral oxybutynin experienced significant improvements in urge incontinence, urinary urgency and enuresis compared with placebo. Urodynamics revealed significant improvements in mean pressure rise on filling and in height of the highest contraction with both placebo and oxybutynin IR. Similar to other studies, anticholinergic adverse effects were problematic and partly invalidated the double-blind nature of the study. Thirty-one women reported adverse effects that could be analysed. Dry mouth was reported by 29 of these patients (94%) during treatment with oxybutynin IR (of which 26 described it as severe) and by 10 patients (32%) during administration of placebo. Constipation was reported by 13 (42%) versus 6 (19%) patients, dry skin by 13 (42%) versus 1 (3%) patient, blurred vision by 8 (26%) versus 1 (3%) patient and nausea by 7 (23%) patients versus no patients during treatment with oxybutynin IR and placebo, respectively (all were $p < 0.05$ for oxybutynin vs placebo). Contact with patients 6 months after the end of the trial indicated that only 7 of the 37 patients enrolled continued to take oxybutynin, but were only able to do so at a reduced dose.[29]

The pharmacokinetics of oxybutynin IR provide an explanation for the tolerability issues experienced by the majority of patients treated with this formulation. Upon ingestion, oxybutynin IR is rapidly absorbed in the small intestine, reaching maximum plasma concentrations within approximately 1 hour (table I).[40,41] Oxybutynin is metabolised by cytochrome P450 (CYP) isozyme 3A4 in the

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gut as well as in the liver to its active metabolite N-desethyl-oxybutynin (N-DEO), and phenylcyclohexylglycolic acid, which is inactive.[41-43] Oxybutynin IR is susceptible to extensive first-pass metabolism in the gut, which results in high serum concentrations of the metabolite. This explains the fact that N-DEO circulates at concentrations approximately 4 to 10 times that of the parent oxybutynin compound.[44-46] This is important because although oxybutynin and N-DEO demonstrate similar activity in the detrusor tissue, their binding affinities in human parotid glands are different.[47] N-DEO has significantly greater binding affinity to the muscarinic receptors on the parotid gland ($pKi = 8.7 \pm 0.1$) than for the bladder tissue ($pKi = 8.5 \pm .1$, $p < 0.05$), which leads to the high incidence of dry mouth.

4.2 Tolterodine IR

Early studies of the IR formulation of tolterodine have demonstrated that this formulation is efficacious in relieving overactive bladder symptoms, but that it also has significant adverse effects. The efficacy and safety of tolterodine IR 2mg twice daily have been evaluated in four randomised, double-blind, placebo-controlled, 12-week studies.[27,50,52,53] Among the combined patient populations, 853 were treated with tolterodine IR and 685 received placebo. Patients ranged between 19 and 93 years of age (mean age 60 years) and were mostly Caucasian (95%) and female (78%). Nearly all participants suffered from urgency and most patients had high urinary frequency and urge incontinence. Results indicate significant increases in void volume per micturition across all four studies, although these reductions did not differ statistically from placebo. The increases in void volume were 36mL ($p < 0.0001$),[27] 38mL ($p < 0.001$),[53] 29mL and 31mL ($p < 0.05$).[50] The number of incontinence episodes decreased considerably in all four studies, although these reductions did not differ statistically from placebo. The respective declines were −1.7/day,[27] −17.7/week,[52] −1.3/day[53] and −1.3 to 1.7/day).[50] Results from phase III clinical trials of tolterodine (2mg twice daily) indicated that dry mouth was reported by 35% of the tolterodine group versus 10% of the placebo group.[50] Constipation was reported by 7% and 4% and headache by 7% and 5%, respectively.

Subsequent comparisons of oxybutynin IR and tolterodine IR, including a meta-analysis, revealed the former to be more efficacious in reducing incontinence episodes and in increasing mean void volume, but with less favourable tolerability.[54] A comparison of the efficacy of oral oxybutynin and tolterodine in reducing urge incontinence episodes in key comparative clinical trials is presented in table II.

Like oxybutynin, tolterodine IR is rapidly absorbed and reaches maximum serum concentrations within 0.5–2 hours after ingestion.[58-60] Tolterodine is metabolised in the liver by CYP2D6 to a 5-hydroxymethyl metabolitev (5-HM) that, like N-DEO, is pharmacologically active.[31,61] Approximately 7% of the population lacks CYP2D6, the enzyme responsible for the formation of 5-HM. The identified pathway of metabolism for these individuals (‘poor metabolisers’) is dealkylation via CYP3A4 to N-dealkylated tolterodine. The majority of the patients (93%) are referred to as ‘extensive metabolisers’. Pharmacokinetic studies revealed that tolterodine is metabolised at a slower rate in

Table II. Mean reduction in urge incontinence episodes across clinical studies comparing oral oxybutynin with tolterodine

Study	Regimen	Oxybutynin (% reduction)	Tolterodine (% reduction)
Appell et al.[55]	Oxybutynin ER, 10mg od; tolterodine IR, 2mg bid	76	68
Diokno et al.[56]	Oxybutynin ER, 10mg od; tolterodine ER, 4mg od	72	70
Abrams et al.[53]	Oxybutynin IR, 5mg tid; tolterodine IR, 2mg bid	71	47[a]
Drutz et al.[57]	Oxybutynin IR, 5mg tid; tolterodine IR, 2mg bid	52[a]	46[a]

a Reduction did not differ statistically from placebo at endpoint.

bid = twice daily; **ER** = extended release; **IR** = immediate release; **od** = every day; **tid** = three times daily.

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poor metabolisers than in extensive metabolisers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HM.[50] However, the safety, tolerability and clinical response are similar in both groups and dose adjustments are not usually needed solely because of metabolism.

Unlike oxybutynin, neither tolterodine nor its metabolite has a high affinity for muscarinic receptors in the parotid gland. The anticholinergic events seen with tolterodine IR were, therefore, assumed to be a result of the high serum peaks achieved with this formulation,[26] meaning that lower peak plasma concentrations would most likely improve tolerability. In addition, the requirement for multiple daily doses could also impact adherence. An evaluation of claims data in patients receiving either oxybutynin IR or tolterodine IR confirmed that >50% of patients discontinued overactive bladder therapy within 6 months.[30] These factors provided the incentive to develop new extended-release (ER) formulations of oxybutynin and tolterodine.

4.3 Trospium Chloride IR

Recently approved by the FDA, trospium chloride has been available for >20 years in Europe.[34] In a randomised, multicentre trial that compared trospium chloride (20mg twice daily) with placebo for 21–24 days in 208 patients with detrusor instability,[62] trospium chloride resulted in significantly improved maximum cystometric bladder capacity ($p = 0.0089$) and volume at first unstable contraction ($p = 0.0124$) compared with placebo. Similar rates of overall adverse events were reported with trospium chloride (68%) and with placebo (62%); however, the incidence of dry mouth was higher with trospium chloride (43 patients) than with placebo (18 patients). There were more reports of headache and dizziness in the placebo group (36 and 15 patients, respectively) than in the trospium chloride-treated group (25 and 11 patients, respectively).

A randomised, double-blind, multicentre trial compared trospium chloride 20mg twice daily with placebo over 12 weeks in 523 patients with overactive bladder.[63] The patients receiving trospium chloride experienced greater improvement in incontinent episodes ($p \leq 0.0001$), average void volume ($p \leq 0.0001$) and the number of daily voids ($p \leq 0.0001$), diurnal voids ($p \leq 0.0001$) and nocturnal voids ($p \leq 0.05$) than patients receiving placebo ($p \leq 0.001$). The incidence of dry mouth was 21.8% in trospium chloride-treated patients compared with 6.5% with placebo; constipation was reported by 9.5% and 3.8% of trospium chloride- and placebo-treated patients, respectively and headaches were reported by 6.5% and 4.6% of patients, respectively. CNS adverse events typically associated with anticholinergic agents were not reported with trospium chloride.

A long-term study compared the tolerability and efficacy of trospium chloride with that of oxybutynin IR in patients with urge syndrome or urge incontinence.[64] In this 52-week trial, trospium chloride (20mg twice daily) and oxybutynin (5mg twice daily) displayed similar efficacy, with reduced micturition frequency, incontinence frequency, urgency and improvement in urodynamic variables. Dry mouth was reported by 50% of oxybutynin IR-treated patients and by 33% of trospium chloride-treated patients ($p < 0.01$).[64]

In contrast to the other available agents, which are negatively charged tertiary amines, trospium chloride is positively charged, which prevents it from crossing the blood-brain barrier and slows its absorption from the gastrointestinal tract.[34] Therefore, trospium chloride is expected to have a low incidence of CNS effects relative to other anticholinergics. When administered twice daily, maximum plasma levels occur 5–6 hours after oral administration and the half-life is 18 hours.[65] Trospium chloride is minimally metabolised by the CYP system, thus limiting its potential for drug-drug interactions.[34] As with other quaternary amines, trospium chloride has low bioavailability, which is overcome by taking the drug on an empty stomach. Twice-daily administration and the recommendation to administer on an empty stomach may be potential disadvantages in terms of compliance.

4.4 Solifenacin IR

Solifenacin 2.5mg, 5mg, 10mg and 20mg daily have been compared with tolterodine 2mg twice daily in patients with overactive bladder in a 12-week, randomised, double-blind, placebo-controlled, multicentre, phase II, dose-finding study.[66] In this study, solifenacin 5 mg/day and 10

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mg/day, but not tolterodine 2mg twice daily, resulted in a significant daily decrease in urgency episodes and incontinence episodes from baseline compared with placebo ($p < 0.001$). Solifenacin 5mg and 10mg reduced daily urgency episodes by 2.85 and 3.07, respectively (both $p < 0.001$ vs placebo). Tolterodine reduced urgency episodes by 2.05 ($p = 0.051$). Daily incontinence episodes decreased by 1.42 ($p = 0.008$) with solifenacin 5mg and by 1.45 ($p = 0.0038$) with solifenacin 10mg. Tolterodine reduced daily incontinence episodes by 1.45 ($p = 0.112$). Both doses of solifenacin and tolterodine resulted in significantly increased mean void volume compared with placebo. The incidence of dry mouth was lowest with solifenacin 5mg (14%) and is similar with solifenacin 10mg (21.3%) and tolterodine (18.6%). The 2.5mg dose achieved numerical but not statistical improvements from placebo. Although the 20mg dose yielded the greatest efficacy, it produced the highest number of adverse events. As a result of this study, solifenacin 5mg and 10mg doses were selected for evaluation in large-scale phase III studies.

Compared with placebo in a randomised, double-blind, placebo-controlled, multicentre clinical trial,[67] solifenacin resulted in fewer micturition episodes (5mg, $p = 0.0018$; 10mg, $p = 0.0001$), fewer urgency episodes (5mg, $p = 0.003$; 10mg, $p = 0.002$), fewer nocturia episodes (5mg, not significant; 10mg, $p = 0.036$) and increased mean void volume (5mg, $p = 0.0001$; 10mg, $p = 0.0001$) from baseline to 12 weeks. The incidence of dry mouth was 7.7% with solifenacin 5mg, 23% with 10mg and 2.3% with placebo. These findings suggest that solifenacin 5 mg/day and 10 mg/day is an effective, well tolerated treatment for overactive bladder.

The selectivity of solifenacin for bladder tissue over parotid gland cells may explain its tolerability. *In vitro* studies conducted in murine bladder and submandibular cells compared the affinity of solifenacin and oxybutynin with that of muscarinic receptors.[68] Although solifenacin and oxybutynin display similar affinity to muscarinic receptors in the bladder, ($pKi = 8.4 \pm 0.13$ and 8.6 ± 0.09, respectively), oxybutynin antagonises the antimuscarinic submandibular gland cells to a much greater degree ($pKb = 7.4 \pm 0.17$ for solifenacin and 8.8 ± 0.21 for oxybutynin). A similar study demonstrated that solifenacin has a weaker affinity for submandibular gland cells isolated from cynomolgus monkeys relative to other antimuscarinics tested (pK*is*: solifenacin = 8.2, tolterodine = 8.7, darifenacin = 8.8, oxybutynin = 9.0).[35] In summary, solifenacin shows receptor selectivity for M_3 subtype receptors over M_2 receptors and tissue preference for the bladder over the salivary gland.

5. Clinical Efficacy and Tolerability of Extended-Release (ER) Antimuscarinics

5.1 Oxybutynin ER

Studies that evaluated oxybutynin ER have demonstrated effective reductions in the symptoms of overactive bladder; however, relative to the IR formulation, decreases in reports of dry mouth and other anticholinergic adverse events were modest.[48,69] In an open-label, single-treatment, 16-centre study, 256 patients (91.4% female, 91.8% Caucasian) with urge or mixed incontinence as determined at baseline were treated with oxybutynin ER at their pre-enrolment oxybutynin IR dose; others were initiated at 5 mg/day.[69] Doses of oxybutynin were adjusted at 5mg increments until the best balance between safety and efficacy was reached or until continence was achieved. Each patient was then treated for 12 weeks at the optimal dose, and efficacy was recorded using 7-day diaries. Oxybutynin ER was associated with an 83.1% mean reduction in urge incontinence episodes (16.0 ± 1.1 episodes per week, 95% CI 13.9, 18.1). Mean weekly micturition frequency decreased from 81.1 ± 1.8 to 66.8 ± 0.4 by the end of the study (mean reduction of 14.3 ± 1.3 micturitions per week, 95% CI 11.7, 16.8). A total of 58.6% of patients reported dry mouth: 35.6% mild and 23.0% moderate or severe in intensity. Only 1.6% of patients actually discontinued therapy because of dry mouth. Nausea caused discontinuation in 2.3% of patients and somnolence in 1.2%. The findings of this study suggest that oxybutynin ER maintains the symptomatic improvement associated with oxybutynin IR, but is associated with a lower incidence of dry mouth.

Anderson et al.[70] compared the efficacy and safety of once-daily oxybutynin ER and oxybutynin IR in a randomised, double-blind, parallel-group,

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multicentre, active control study that included 97 women and 8 men with urge or mixed incontinence. Doses of both formulations were initiated at 5 mg/day and were increased to a maximum allowable dose of 20mg for oxybutynin IR or 30mg for oxybutynin ER, until maximum efficacy and tolerability were achieved. The two formulations of oxybutynin demonstrated similar efficacy. The number of weekly urge incontinence episodes decreased from 27.4 to 4.8 with oxybutynin IR and from 23.4 to 3.1 with oxybutynin ER ($p = 0.56$). Total incontinence episodes declined from 29.3 to 6 and from 26.3 to 3.8, respectively ($p = 0.6$). Continence was achieved in 41% of the patients who received oxybutynin ER and 40% of those who received oxybutynin IR ($p = 0.9$). However, there was a significant difference in the incidence of dry mouth in patients receiving the two agents. Dry mouth was reported by 68% of patients who received oxybutynin ER and 87% of those treated with the IR formulation ($p = 0.04$). The incidence of other anticholinergic adverse events did not differ statistically between the IR and ER formulations. Somnolence was reported by 38% of those receiving oxybutynin ER and 40% of those receiving oxybutynin IR ($p = 0.8$) and constipation was reported by 30% and 31%, respectively ($p = 1.0$). The results of this study suggest that the use of oxybutynin ER may lead to a reduced incidence of dry mouth, but further reductions in other anticholinergic adverse events than that obtained with this formulation are still desirable.

In another prospective, randomised, double-blind study of patients with overactive bladder ($n = 378$), the efficacy and tolerability of oxybutynin ER 10 mg/day were compared with those of tolterodine IR 2mg twice daily.[55] By the end of this 12-week study, patients receiving oxybutynin ER achieved greater reductions in urge incontinence episodes (end of study values = 6.1 ± 9.7 episodes per week with oxybutynin vs 7.8 ± 11.1 mean episodes per week in tolterodine group, $p = 0.03$), total incontinence (7.1 ± 12.0 vs 9.3 ± 13.4 mean episodes per week, $p = 0.02$) and urinary frequency (67.1 ± 22.1 vs 71.5 ± 20.5 mean episodes per week, $p = 0.02$) than did patients receiving tolterodine IR.[55] However, tolerability of the two agents was similar. All CNS adverse events, dizziness, insomnia, nervousness and somnolence, occurred with similar frequency in both groups. Dry mouth was reported by 52 of 185 (28.1%) patients receiving oxybutynin ER and by 64 of 193 (33.2%) patients treated with tolterodine IR ($p = 0.32$). Approximately 10% of patients in each group reported that the dry mouth was moderate to severe. The overall discontinuation rates due to adverse events was similar between the two groups (7.6% in the oxybutynin ER group vs 7.8% in the tolterodine group, $p = 0.99$). The findings of this study suggest that oxybutynin ER may be statistically more effective than tolterodine ER, although the clinical significance of this difference may vary between patients or between patient populations. The two agents appear to have similar tolerability in the formulations compared.

To provide controlled delivery, oxybutynin was incorporated into the OROS® [1] osmosis technology tablet. OROS® technology involves an osmotically active component behind the drug reservoir that 'pushes' oxybutynin through a small, laser-drilled opening. As the pill passes through the aqueous environment in the gastrointestinal tract, the osmotic push element drives the delivery of oxybutynin.[56] The pharmacokinetics of oral oxybutynin ER was compared with that of the IR formulation in a randomised, open-label, two-way, crossover, multiple-dose study. With the gradual release of the active component via OROS® technology, initial doses of oxybutynin ER (three 5mg tablets administered once daily) have lower (maximum plasma concentration [C_{max}] = 4.2 ng/mL) and delayed (mean time to C_{max} [t_{max}] = 13.2h) maximum plasma concentrations of oxybutynin compared with those of oxybutynin IR (5mg administered three times per day) [C_{max} = 12.0 ng/mL; t_{max} = 3.2h].[48] This is also true for serum concentrations of the primary metabolite, N-DEO. The average apparent elimination half-life ($t_{1/2}$) values estimated for oxybutynin ER are also longer than those calculated for oxybutynin IR, presumably due to, at least in part, slower drug absorption.

In summary, the ratio of oxybutynin to N-DEO is considerably higher for the oxybutynin ER for-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

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mulation (0.40) than for the oxybutynin IR formulation (0.18).[48] Therefore, serum concentrations of N-DEO are lower following oral administration of oxybutynin ER relative to the IR formulation. This difference is likely attributable to the release of oxybutynin farther along the gastrointestinal tract, particularly in the colon, with this formulation, thus bypassing much of the initial presystemic CYP-mediated oxidation that takes place in the small intestine.[48]

5.2 Tolterodine ER

As with oxybutynin, the ER formulation of tolterodine provides advantages over the IR preparation. A large (n = 1529), 12-week, double-blind study that compared tolterodine ER 4mg once daily, tolterodine IR 2mg twice daily and placebo demonstrated that both formulations provide significantly improved symptom control relative to placebo.[26] Tolterodine ER reduced the weekly number of incontinence episodes by 11.8 ($p = 0.0001$ vs placebo), while tolterodine IR did so by 10.6 episodes per week ($p = 0.0005$ vs placebo). There were also significant reductions in the number of voluntary micturitions (−1.8 per day for tolterodine ER vs −1.7 for tolterodine IR, each $p \leq 0.0005$ vs placebo), total micturitions (−3.5 and −3.3 per day, each $p \leq 0.0002$ vs placebo) and increases in void volume per micturition (34mL and 29mL, each $p < 0.0001$ vs placebo). The most frequently occurring adverse event was dry mouth, which was reported by 23% of the group receiving tolterodine ER 4mg daily, by 30% of the group receiving tolterodine IR 2mg twice daily and by 8% of the placebo group. Tolterodine ER may possess improved efficacy relative to the IR formulation. It does demonstrate a lower incidence of dry mouth.

The efficacy and tolerability of the ER formulations of oxybutynin and tolterodine were compared in another 12-week, double-blind trial involving women with urinary urge incontinence (n = 790).[56] Documentation of 21–60 urge urinary incontinence episodes per week and 10 or more voids per day were required at baseline. Both treatment groups showed clinically similar improvements in urge urinary incontinence episodes from baseline over the 12-week treatment period.[56] However, relative to tolterodine ER, oxybutynin ER was significantly more effective in reducing micturition frequency. In addition, the portion of patients reporting complete dryness (no incontinence episodes) in the last week of the trial with oxybutynin ER (23%) was significantly higher than with tolterodine ER (16.8%, $p = 0.03$). Again, dry mouth was the most commonly noted adverse event and was reported by 29.7% of the oxybutynin ER group and 22.3% of the tolterodine ER group ($p = 0.02$). Other typical anticholinergic adverse events, such as constipation, blurred vision, urinary retention and CNS adverse events (e.g. dizziness, somnolence and depression) occurred with similar frequency in both groups (<5% of patients). Reduction in the incidence of dry mouth may be due to the more steady delivery of tolterodine provided by the ER formulation.[26]

The ER formulation of tolterodine was developed to improve tolerability and to simplify administration relative to the IR formulation. Tolterodine ER is a capsule of identical tolterodine ER beads. Each bead has an insoluble bead core surrounded by a prolonged-release layer, which is comprised of 85% ethyl cellulose. Tolterodine slowly dissolves through this semipermeable polymer, with each bead providing a prolonged release of the compound over the 24-hour administration interval. A small amount of the bead is insoluble and exits the body through the stool. Like the IR formulation, tolterodine ER undergoes extensive metabolism in the liver mediated by CYP2D6, which yields 5-HM. However, compared with the 2mg twice-daily dosage, a single dose of the 4mg ER dose yields a lower C_{max} (about 75% of the IR C_{max}), a longer t_{max} (2–6 hours compared with 1–2 hours with the IR formulation) and a minimum concentration (C_{min}) that is 1.5 times higher than that of the IR formulation.[50,51] These factors may be responsible for the amelioration of adverse events. Because the metabolite does not have higher affinity for the parotid gland, as occurs with oxybutynin, the incidence of dry mouth with tolterodine IR is lower than that of oxybutynin ER.

5.3 Darifenacin ER

Darifenacin is the most recently approved agent for treating overactive bladder. In a pooled analysis of three 12-week, double-blind, placebo-controlled trials of darifenacin in 1049 patients, darifenacin

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7.5mg and 15mg demonstrated significantly greater improvement in all efficacy measures than placebo.[71] Dry mouth occurred in 20% of patients treated with darifenacin 7.5mg and 35% of those treated with darifenacin 15mg; CNS and cardiovascular safety was comparable to that of placebo.[71] Subanalyses of these data found similar efficacy and safety in older adults (aged ≥65 years),[72] along with improvement in nocturia.[73] The selectivity profile of this agent provides an explanation for its good tolerability.

Darifenacin has demonstrated greater *in vitro* selectivity for the M_3 receptors on the salivary gland relative to traditional agents.[38] In a study of darifenacin, oxybutynin, tolterodine and atropine, atropine demonstrated equal potency against the bladder and salivary glands, while oxybutynin and tolterodine demonstrated selectivity for the bladder over the salivary gland (3-fold and 5-fold, respectively). However, darifenacin was 9-fold more potent on the bladder than on the salivary gland; therefore, theoretically, darifenacin-treated patients should report less severe dry mouth relative to oxybutynin. However, this theory was not replicated in similar magnitude in clinical trials. To allow once-daily administration, thus increasing convenience, the active ingredient has been embedded in an insoluble matrix that leaks out as it traverses the intestine. Darifenacin is administered once daily with liquid and can be taken with or without food. Its use is not recommended for patients with severe hepatic impairment.

Although the most recently approved oral agents, trospium chloride, solifenacin and darifenacin, demonstrate improved tolerability relative to oxybutynin IR, dry mouth is still reported in >20% of patients. Dry mouth is reported by 27.6% of patients treated with solifenacin 10mg, by 35.3% of patients treated with darifenacin 15mg and by 20.1% of patients treated with trospium chloride 20mg twice daily.[65,74,75] It may, therefore, be worthwhile to consider formulations of oxybutynin that avoid first-pass metabolism, thereby yielding lower levels of the active metabolite N-DEO, which has been linked to anticholinergic adverse events in patients treated with oxybutynin.

6. Formulations that Avoid First-Pass Metabolism

6.1 Delivery Methods

6.1.1 Transdermal Delivery

With the oxybutynin transdermal delivery system (TDS), oxybutynin is delivered through the skin to the bloodstream via a slim matrix-type system (figure 2) and is able to bypass gastric and hepatic first-pass metabolism, thereby decreasing metabolism to N-DEO. This results in an average oxybutynin/N-DEO plasma concentration ratio that is less than that seen with oral oxybutynin delivery.[46,76,77] This correlates with quantifiable reductions in N-DEO-associated adverse effects, as demonstrated in clinical trials.

The efficacy and tolerability of the oxybutynin TDS have been evaluated in several clinical trials.

In a short-term, randomised, double-blind, multicentre, dose-titration study, the safety and efficacy of oxybutynin TDS (up to 5.2 mg/day) were compared with oral oxybutynin (up to 7.5mg three times daily) in 76 patients with a history of urge or mixed urinary incontinence.[79] Thirty-eight patients were randomised to each treatment. All patients had responded to oxybutynin IR in the past, necessitating a 2-week washout phase followed by a 6-week titration and treatment phase. Efficacy was determined using a 3-day diary and a visual analogue scale. Because dose titration was based on tolerability, a

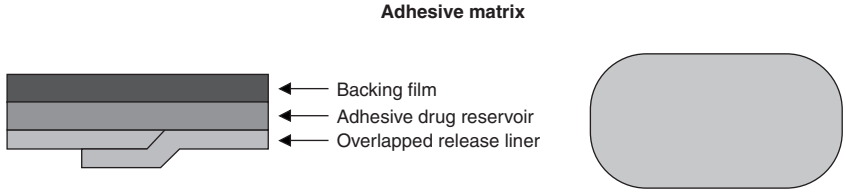

Fig. 2. Components of the transdermal system. The oxybutynin transdermal delivery system is an adhesive matrix system (reproduced with permission from Watson Pharma, Inc.[78]).

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patient questionnaire was developed to document the occurrence and severity of anticholinergic symptoms. Both treatments reduced the incidence of incontinence episodes (oxybutynin TDS from 7.3 to 2.4 times per day; oxybutynin IR from 7.4 to 2.6 times per day; p = 0.39) A total of eight patients in the group that received transdermal oxybutynin and ten patients that received the IR formulation reported no incontinence episodes upon completion of the study. The difference between the two treatments in the mean visual analogue scale score of overactive bladder symptoms following treatment was insignificant (0.1cm, p = 0.9). Average bladder volume at first contraction increased by 66mL for the patients who received oxybutynin TDS (p = 0.0011 vs baseline) and by 45mL for those treated with oral oxybutynin (p = 0.0538 vs baseline).

Regarding efficacy, there was no significant difference between the two treatment groups (p = 0.57).[79] However, the tolerability profiles differed, with patients in the transdermal group having milder and fewer adverse effects. Following upward titration based on tolerability, 39% of the TDS group and 94% of the oral group (p < 0.001) reported dry mouth. Dry mouth was rated as absent, mild, tolerable or intolerable by 62%, 27%, 11% and 0%, respectively, of the patients who received transdermal oxybutynin. The respective values for the patients treated with oral oxybutynin were 6%, 26%, 59% and 9%. In addition, 67% of patients who received transdermal TDS indicated that their current therapy resulted in reduced severity of dry mouth versus prior treatment. Only 33% of patients treated with oxybutynin IR made similar claims. Constipation was reported by 21% of the transdermal group and by 50% of the oral group. Nausea was reported by 8% and 26%, respectively. These differences in tolerability impacted dose titration during the study. Up to 68% of patients in the transdermal group reached the maximum dose available during the study compared with 32% of patients in the oral group. Transdermal oxybutynin proved to be as efficacious, but was more tolerable than oxybutynin IR in this study.

In another randomised, double-blind study, 520 patients with a history of overactive bladder were randomised to receive oxybutynin TDS 1.3 mg/day, 2.6 mg/day or 3.9 mg/day or a placebo patch applied twice weekly for 12 weeks.[80] Patients had to report ≥10 incontinence episodes and ≥56 weekly voids in a 7-day diary at baseline to be included in this study. The primary efficacy variable was the change in the number of incontinence episodes per week. Patients were monitored for symptoms, quality of life and treatment tolerability. The 3.9mg transdermal dose provided a significant improvement (decrease) in incontinence episodes per week (median change −19.0) compared with placebo (median change −14, p = 0.065) and in average daily urinary frequency (median decrease −2) compared with placebo (median change of −1, p = 0.03) during the 12-week, double-blind period. The incidence of anticholinergic adverse events was similar between transdermal oxybutynin 3.9 mg/day and placebo. Dry mouth was reported by 9.6% and 8.3%, dizziness by 4.0% and 3.8% and dysuria by 2.4% and 0%, respectively. The most common adverse events noted were application site reactions, with the majority being mild to moderate in intensity. Erythema occurred in 5.6% of patients on the 3.9 mg/day patch and in 2.3% of the placebo group. Pruritus was reported by 16.8% of the active treatment group and by 6.1% of the placebo group.

Another double-blind, double-dummy trial was conducted to compare the safety and efficacy of transdermal oxybutynin, tolterodine ER and placebo.[25] Treatment-experienced patients with urge or mixed incontinence (n = 361) had their previous therapy withdrawn and were randomised to receive oxybutynin TDS 3.9 mg/day (applied twice weekly), tolterodine ER 4 mg/day or placebo for 12 weeks. The two active treatment groups were similar in terms of efficacy. There was a 75% reduction in incontinence episodes in the two groups receiving active treatment compared with a 50% improvement in the placebo group (p < 0.05 for each active treatment vs placebo). A total of 120 patients had no incontinence episodes at study endpoint: 47 patients receiving transdermal oxybutynin (39%), 47 receiving tolterodine (38%) and 26 in the placebo group (22%). Median increases in average void volume were 24mL in the transdermal group (p = 0.0010 vs placebo), 29mL in the tolterodine group (p = 0.0017) and 5.5mL in the placebo group. Daily micturition frequency decreased in the transdermal oxybutynin (median change −2, p = 0.10 vs placebo)

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and tolterodine groups (median change −2; p = 0.0025 vs placebo) and in the placebo group (median change −1). Although the decrease in micturition frequency in the group receiving tolterodine was statistically significant, the difference between the two treatment groups was not significant (95% CI −1, 0; p = 0.276) Application site reactions were more common in the transdermal oxybutynin group while treatment-related systemic adverse events were more frequent in the tolterodine group. As in the previous study, the most common application site reactions were pruritus (14.0% with transdermal vs 4.3% with placebo) and erythema (8.3% with transdermal vs 1.7% with placebo). Of the 32 incidences of application site reactions in the transdermal group, 26 were mild-to-moderate in intensity. Dry mouth was reported by 4.1% of patients receiving oxybutynin TDS (p = 0.268 vs placebo), 7.3% of patients receiving tolterodine ER (p = 0.038 vs placebo) and 1.7% of patients receiving placebo.[25] These studies demonstrated the fact that the transdermal formulation of oxybutynin maintains the efficacy associated with the oral formulations, but is associated with a lower incidence of systemic anticholinergic adverse events.

The pharmacokinetic characteristics of oxybutynin and N-DEO delivered via this formulation were assessed in a clinical study conducted in 24 healthy volunteers.[46] It was observed that oxybutynin appears in the plasma about 2 hours following an initial application of the patch. Plasma concentrations of the parent compound and the metabolite gradually increase over 24–36 hours, after which the concentrations remain stable for approximately 24 hours, tapering slightly downward over the next 96 hours. Serum concentrations of N-DEO are only 1.5 times greater than mean oxybutynin concentrations. The median C_{max} of the parent compound is similar, regardless of whether the system is applied to the abdomen (3.4 ± 1.1 ng/mL), hip (3.7 ± 1.3 ng/mL) or buttock (4.0 ± 1.5 ng/mL). Median t_{max} values for the parent compound are also similar between the three application sites. The bioequivalence at multiple application sites provides flexibility and may be used to increase local tolerability.

Pharmacokinetics, metabolism and saliva output during treatment with transdermal oxybutynin were compared with those of oxybutynin ER in healthy patients in a second, randomised, two-way, crossover study (6-day duration for each treatment) in which 13 healthy participants (7 women and 6 men) were administered a twice-weekly TDS or a single daily dose of oral oxybutynin ER 10mg.[77] Venous blood samples were collected at baseline and periodically throughout the study period. Saliva output over a period of 2 minutes was also assessed every 12 hours after the application of the second transdermal system and after the third oral ER tablet. Exposure to oxybutynin was comparable with the two formulations (10.8 ± 2.4 $ng \bullet h^{-1} \bullet mL^{-1}$ with transdermal oxybutynin vs 9.2 ± 3.3 $ng \bullet h^{-1} \bullet mL^{-1}$ with oxybutynin ER). However, concentrations of N-DEO were significantly lower after transdermal administration than with oral oxybutynin ER (p < 0.001). Mean salivary output was significantly greater during transdermal therapy (15.7 ± 9.3g) than with oral oxybutynin ER (12.2 ± 6.8g, p = 0.02). Saliva output was consistently greater at each measurement. Regression analysis revealed significant correlation between N-DEO levels and salivary output (r = −0.59, p = 0.04). In contrast, the correlation between oxybutynin concentrations and saliva output was not statistically significant. The findings of this study thus confirm that transdermal delivery of oxybutynin results in clinically relevant changes in pharmacokinetics, metabolism and pharmacodynamic effects of oxybutynin compared with oral administration. The transdermal system, therefore, provides a treatment option for patients who find oral antimuscarinics intolerable, those who already take several other pills a day and patients who do not wish to administer their medication on a daily basis.

6.1.2 Rectal Delivery

Intrarectal oxybutynin has been shown to be effective and more tolerable than oral oxybutynin. In a clinical study,[81] 20 patients with clinically proven detrusor muscle instability who could not tolerate oral oxybutynin at a dosage of 5mg twice daily were administered the intrarectal formulation at the same dose. During their initial treatment with oral oxybutynin, 15 patients (75%) complained of dry mouth of varying intensity. After switching, dry mouth was reported by only 13.3% of patients. Five patients (25%) became completely continent, while others reported significant reductions in symptoms after the 1-month study period. The findings of this

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study suggest that intrarectal oxybutynin is likely to be efficacious and tolerable in some patients with symptoms of overactive bladder.

Another retrospective review of the charts of 25 women with detrusor instability, who were treated with intrarectal oxybutynin given at dosages ranging from 5mg to 20mg daily, yielded differing results.[82] All of the patients had previously failed to tolerate oral oxybutynin or other anticholinergic agents; oral oxybutynin in particular had been tried by 80% of patients. Nine women (36%) reported >50% global symptom improvement, while 12% noted some improvement following use of the intrarectal oxybutynin. However, 48% reported dry mouth and 14.3% reported constipation. Intrarectal oxybutynin provides an efficacious alternative to oral oxybutynin for patients who find the latter intolerable, but it appears that many patients may still experience adverse events, albeit a smaller proportion than is observed with oral oxybutynin.

Rectal administration of oxybutynin has been demonstrated to have gradual absorption (t_{max} 4 hours vs 45 minutes for oral oxybutynin) and relatively constant plasma concentrations (mean 1.17 ng/mL over 12 hours), which are actually higher than those observed after oral administration ($p < 0.05$). Because a drug administered via this route does not pass through the portal system before entry into the circulation, the production of the metabolite N-DEO is much less and results in fewer, less severe adverse events.[83] There are no commercial preparations of oxybutynin rectal suppositories available.

6.1.3 Intravesical Delivery

Intravesical delivery (delivery directly into the bladder) of oxybutynin has also been investigated as a means of bypassing first-pass metabolism and reducing the adverse effects associated with the metabolite of oxybutynin. A solution is compounded by crushing 5mg tablets of oxybutynin and dissolving them in distilled water.[45,84] This solution is then instilled in the bladder using a catheter. This method is usually considered in patients with neurogenic causes of bladder instability, such as multiple sclerosis or myelodysplasia, in whom indwelling or intermittent catheters are used to treat urinary dysfunction.

The efficacy and tolerability of intravesical oxybutynin have been evaluated in several trials. In a study of 42 patients who were incontinent and had failed oral anticholinergic therapy, aqueous oxybutynin solution was administered 2–3 times daily via clean self-intermittent catheterisation.[84] No adverse effects were reported after 18 months of treatment and 55% of patients experienced elimination or a significant reduction in their incontinence with a mean decrease of 2.5 protective urinary pads per day. However, >21% of patients did not complete the study because of difficulties associated with self-catheterisation or with retaining the solution in the bladder. Subsequently, a modified form of intravesical oxybutynin that would require less frequent administration was developed.

Modified intravesical oxybutynin (intravesical oxybutynin with hydroxypropylcellulose) in a concentration of 5mg/10mL was administered twice daily to six patients diagnosed with neurogenic bladder who did not respond to oral anticholinergics (oxybutynin or propiverine) or electrical stimulation therapy.[85] Cystometography performed before and 1 week after intravesical oxybutynin administration revealed that bladder capacity had significantly increased from a mean of 141.8 ± 15.3mL before treatment to a mean of 305.0 ± 21.3mL after 1 week of treatment ($p < 0.05$). Uninhibited contractions ceased in two of the six patients. Four patients rated the therapy as excellent, while the remaining two patients rated intravesical oxybutynin as good. No adverse effects were observed during the study. Although conducted in a small population, the findings of this study suggest that intravesical oxybutynin administration should be considered as another treatment option, although not a very convenient one, for the treatment of neurogenic bladder.

As with other advanced formulations of traditional agents, the pharmacokinetic profile for intravesical oxybutynin provides an explanation for its improved tolerability.[45] Plasma concentrations of oxybutynin and its metabolite were determined at steady state following multiple-dose administration of oral oxybutynin to 5 patients and intravesical oxybutynin to 11 patients. Oral oxybutynin at a dose of 0.2 mg/kg results in peak plasma N-DEO concentrations that are 7.4 ± 1.3 times higher than the corresponding oxybutynin levels. Following intravesi-

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cal instillation of the same dose, N-DEO concentrations are only 1.2 ± 0.1 times higher than concentrations of the parent compound. This reduction in first-pass metabolism, as seen with ER formulations as well as with rectal administration, is the likely explanation for the increased tolerability of oxybutynin administered via this route. The improved systemic tolerability and proven efficacy associated with this formulation has encouraged further research into easier methods of intravesical delivery. The ideal system would be small enough to avoid bladder irritation and large enough to remain in the bladder. One such system in development by UROS (San Diego, CA) involves a small balloon reservoir that delivers a drug for 28 days, at which point it can be retrieved using a flexible cystoscope and replaced.[86]

7. Future Prospects for Improved Tolerability of Anticholinergics

7.1 S-Oxybutynin

Studies have shown that the two enantiomers of oxybutynin, the R and S isomers, have different binding affinities for the muscarinic receptors, with the R isomer having a much higher affinity for the M_3 receptor than the S isomer. When evaluating the effects of the two isomeric forms on antispasmodic activity, it was found that both forms have similar antimuscarinic activity, with the R isomer being a more potent antimuscarinic and the S isomer having more prominent spasmolytic activity.[87] Based on this rationale, it was theorised that treatment with monomeric S-oxybutynin may allow for antispasmodic activity, while minimising the anticholinergic adverse effects. In a 12-week study involving more than 650 patients, S-oxybutynin at a dosage of 120mg three times daily yielded a significant improvement in the reduction of combined micturitions (voluntary and involuntary) and number of patients achieving complete continence, compared with placebo.[88]

7.2 M_2-Selective Antimuscarinics

Although M_3 receptors have been documented as playing a prominent role by mediating direct bladder contraction, M_2 receptors are more abundant. In addition, M_2 receptors are not located on the parotid gland. Following this rationale, it has been hypothesised that an M_2-selective inhibitor would be an ideal candidate for treating overactive bladder, while avoiding dry mouth.[14,89] It has been proposed that the importance of these M_2 receptors in bladder contraction may be increased following neurological injury. Therefore, it is expected that an agent that selectively inhibits these receptors will be developed in the near future for the treatment of idiopathic detrusor instability, as well as instability due to neurogenic causes.

8. Conclusion

Improvements in formulation and changes in mode of delivery have led to reduced administration frequency and improved tolerability of anticholinergics. The two most commonly used antimuscarinics, oxybutynin and tolterodine, were first introduced as IR formulations that required administration two or three times daily. Both drugs are now available in ER formulations that permit once-daily administration. This has increased the convenience of treatment and has reduced the incidence and severity of dry mouth, but the incidence of other anticholinergic adverse events is still prevalent with oxybutynin ER. Oxybutynin is now also available in a TDS that is applied twice weekly. This preparation not only enhances convenience, it also decreases the occurrence of dry mouth and other systemic anticholinergic adverse effects. Results of pharmacokinetic and pharmacodynamic studies showed that N-DEO, the active metabolite of oxybutynin, was in large part responsible for the adverse effects of oxybutynin and the newer formulations were designed to decrease serum concentrations of this metabolite. The ER formulation of oxybutynin reduced the ratio of N-DEO to the parent drug and the transdermal preparation produced an even greater improvement in this measure, resulting in an anticholinergic safety profile similar to that of placebo.

The recent approval of new anticholinergic agents in the US has increased treatment options for patients with overactive bladder. Some agents target bladder tissue (e.g. solifenacin, darifenacin), while one new agent, trospium chloride, does not readily cross the blood-brain barrier. All of the newly approved oral agents have demonstrated an efficacy

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similar to traditional agents. Unfortunately, none of these agents has demonstrated a significantly superior anticholinergic adverse effect profile, particularly in reducing troublesome dry mouth, relative to oxybutynin ER and tolterodine ER. Increased understanding of muscarinic receptor subclasses and their roles in bladder and other tissues will most likely lead to further expansion in the armamentarium of pharmacological treatments for overactive bladder.[57]

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