Trospium chloride: over 20 years of clinical use

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Antimuscarinic drugs currently form the mainstay of pharmacotherapy for overactive bladder. Trospium chloride, an antimuscarinic with an unusual quaternary amine structure, has recently gained approval in the USA for the treatment of this condition. As a quaternary amine, trospium has pharmacological properties that are distinct from other available antimuscarinics and which contribute to its salutary safety and efficacy profile. Limited ability to cross the blood–brain barrier minimizes the potential for centrally mediated adverse events. Metabolism independent of the cytochrome P450 isoenzyme system allows confident prescription of trospium alongside the majority of commonly used drugs. The presence of unchanged trospium in the bladder – the primary therapeutic site of action – may contribute to pharmacological activity, providing earlier onset and improved and prolonged efficacy compared with other, more extensively metabolized antimuscarinic agents.

Overactive bladder (OAB) is a condition characterized by the symptoms of urinary frequency and urgency, with or without urge urinary incontinence (UUI) and nocturia [1]. OAB can have a significant detrimental effect on physical functioning and psychological wellbeing and can significantly reduce quality of life (QoL) [2–4]. The prevalence of OAB increases significantly with age in both men and women: over 33 million individuals are thought to be affected by the disorder in the USA alone, with over 12 million individuals experiencing UUI [4,5]. In addition to reducing patients' QoL, OAB can impose a significant financial burden, with OAB patients demonstrating reduced productivity while at work and requiring more sick leave than those without OAB [6,7]. The condition is also associated with a variety of health-related consequences, including urinary tract infections, falls and fractures, and it has been suggested as a precipitating factor for nursing-home admission [7,8].

The pathophysiology of OAB appears to be multifactorial, involving abnormalities of the peripheral nervous system and/or CNS, the urothelium lining the bladder and/or the detrusor muscle [9–13]. Both afferent and efferent neural pathways are involved in the regulation of normal micturition, in conjunction with a variety of central and peripheral neurotransmitters. Most notable of these neurotransmitters is acetylcholine, which binds to muscarinic receptors in the detrusor muscle, thereby facilitating bladder contraction. The role of sensory afferent pathways has gained increasing attention in recent years, both in the normal control of bladder contraction and the pathological states, such as OAB. Afferent nerves are known to lie in proximity to the urothelium and are involved in sensory feedback to the brain [13–15]. Changes in the structure or function of the sensory afferent nerves to the urinary bladder or abnormalities in the sensory feedback mechanisms that regulate the normal micturition process may result in the symptoms of OAB.

Therapy overview

Nonpharmacological approaches, such as behavioral modification, bladder retraining and pelvic floor exercises, are used in the management of OAB [16,17]. However, pharmacotherapy – in particular with antimuscarinic agents, including oxybutynin, tolterodine, trospium, and more recently, solifenacin and darifenacin – currently forms the mainstay of therapy for adults with OAB. As a class, these agents are thought to prevent involuntary detrusor contractions through their inhibitory effects on muscarinic receptors in detrusor smooth muscle, presynaptic nerve terminals and possibly at sensory afferent nerve terminals in or beneath the urothelium itself [18–20]. Given their potent effects on muscarinic receptors throughout the body, there have been safety concerns with regard to the potential for these agents to penetrate the CNS, where they could theoretically impair cognitive performance [21–23]. Other safety concerns surrounding antimuscarinic therapy have been the potential for

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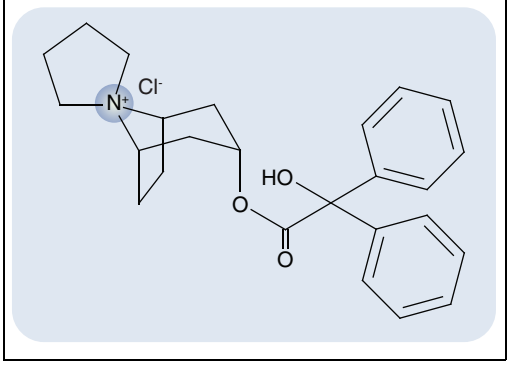
Figure 1. Chemical structure of trospium, with the quaternary ring highlighted.



drug–drug interactions and peripheral adverse effects, notably dry mouth and constipation.

Introduction to the compound

Trospium chloride has been available in Europe as a treatment for OAB for over 20 years and has recently become available in the USA for this indication. The chemical structure of trospium, a quaternary amine, is distinct among the currently available antimuscarinic agents, which are tertiary amines. Its structure results in distinct physicochemical properties, which in turn contribute to a pharmacological profile that in many aspects is unique among the available antimuscarinic agents. In particular, it is believed that trospium, like other quaternary amines, has little or no ability to cross the blood–brain barrier (BBB), which most likely contributes to the lack of CNS adverse effects associated with this agent.

Chemistry

Trospium (azonia-spiro[3-α-benziloyl-oxy-nortropane-8,1′-pyrrolidinium]-chloride) is a positively charged, hydrophilic, quaternary ammonium derivative of atropine (**Figure 1**).

Pharmacokinetics/pharmacodynamics

Absorption

Absorption of trospium in the gut is a complex and poorly defined process. *In vitro* experiments with rat jejunum and human Caco-2 cells suggest that the process may involve P-glycoprotein excretion and saturable binding to intestinal mucus [24]. The role of P-glycoprotein and other drug transporters has, however, not been investigated *in vivo*. Less than 10% of an oral dose of trospium is absorbed via the gastrointestinal tract and a 20 mg oral dose has an absolute bioavailability of approximately 10% (**Table 1**) [28]. This is likely due to the hydrophilic nature of the drug (a consequence of its quaternary amine structure) [29], which makes it difficult for this agent to pass through the lipophilic intestinal epithelium. Peak plasma levels of trospium are reached 5–6 h after oral dosing (**Table 1**) (**Figure 2**) [25,26,101].

Distribution

The extent of trospium binding to plasma proteins ranges from 50–85% in *in vitro* studies using therapeutic drug concentrations (**Table 1**) [25]. The majority of absorbed trospium is distributed systemically in plasma, and trospium does not appear to accumulate in tissues following repeated oral administration. Studies in which rats were given radioactively labeled [^{14}C]trospium at 20 mg/kg showed that the majority of the radioactivity remained in the gastrointestinal tract and the absorbed radioactivity did not appear to cross into the CNS. The lack of penetration of trospium across the BBB is likely to be as a result of its quaternary amine structure, resulting in low lipophilicity and ionization at a neutral pH [24,30]. Clinical evidence from electroencephalography (EEG) and sleep studies also indicates that there is no appreciable distribution of trospium into the CNS [31–34].

Table 1. Pharmacokinetic profile of trospium [25–28].

Characteristic	Value
C_{max} (following 20 mg dose)	3–4 ng/ml
T_{max}	5–6 h
Bioavailability	~10%
Elimination half-life	12 h
Protein binding	50–85%
Renal elimination	70%
Metabolic drug interactions	None
Proportion of absorbed compound excreted in unchanged (active) form in urine	60–80%

Effect of trospium on bladder smooth muscle contraction & function

Both *in vitro* and *in vivo* studies have demonstrated the ability of trospium to reverse cholinergically induced bladder smooth muscle contraction [45–48]. In *in vitro* studies, trospium has been shown to cause relaxation of cultured detrusor myocytes [47] and to effect a dose-related reversal of cholinergically-induced porcine and human bladder smooth muscle contractions [45,46]. Intravenous administration of trospium to healthy adult volunteers has been shown to reduce bladder pressure that has been artificially elevated by choline citrate administration [48].

Clinical efficacy

Trospium in placebo-controlled studies

Two pivotal, placebo-controlled studies have been conducted in the USA among adults (aged ≥18 years) with OAB of at least 6 months duration (**Table 3**) [49,50]. Subjects with OAB and UUI were randomized in a double-blind trial to receive either placebo or trospium 20 mg twice daily for up to 12 weeks. In both studies, trospium 20 mg twice daily demonstrated significant and sustained effectiveness from week 1 onwards in reducing the number of toilet voiding episodes/day, reducing the number of UUI episodes/day, increasing the volume/void, and decreasing the urgency severity compared with placebo. Detailed analysis of one of the studies indicated that trospium provided statistically significant improvements in efficacy over placebo in end points (toilet voids, urgency severity/void) within a few days of treatment initiation [51]. For UUI and OAB-Symptom Composite Score (SCS), statistically significant improvements over placebo were observed at day 1 [51]. Trospium was associated with significant improvements in QoL compared with placebo at week 12 in both studies ($p \leq 0.05$). Subjects who took part in the first of these two studies [49] were given the option to continue their treatment for a further 9 months [52]. A total of 407 men and women continued treatment with trospium 20 mg twice daily and 65% completed the 9-month extension phase of the study. Efficacy reported in the initial 3 months of the study by subjects randomized to trospium – including reductions in frequency and UUI episodes and an increased volume voided – was maintained throughout the 9-month extension phase [52].

A *post hoc* analysis has recently been reported using a newly developed and validated OAB-SCS. This scale combines frequency, urgency severity, and UUI episodes, and may be more sensitive to subtle changes in OAB disease state than individual symptoms alone [53]. In a pooled analysis of data for 1157 subjects who took part in one of the two Phase III US-based studies described above, men and women were assigned OAB-SCS scores for each of the 7-day diary collection periods at weeks 1, 4 and 12. Scores were based on urgency severity associated with each toilet void and the number of UUI episodes in which the subject did not reach the toilet in time. Subjects treated with trospium experienced a mean improvement of 10 points over the 12-week study period compared with a mean improvement of 5 points among those who received placebo (**Figure 4**).

In two European trials of subjects with cystometrically confirmed detrusor overactivity, trospium produced significant improvements in the maximum cystometrically assessed bladder capacity and urinary volume at the first unstable contraction (**Table 4**) [54,55]. In these studies, participants also gave an assessment of perceived efficacy and reported significantly greater clinical improvement in the trospium group compared with the placebo group ($p < 0.0001$ for both studies [54,58]).

Trospium in active comparator-controlled studies

Trospium appears to offer comparable efficacy to other currently available antimuscarinic agents commonly used for the treatment of detrusor overactivity. In a 3-week study among subjects with urodynamically verified detrusor overactivity, trospium 20 mg twice daily produced statistically significant improvements in daily micturition frequency compared with the placebo group, while those subjects in the tolterodine 2 mg twice daily arm did not demonstrate statistically significant improvements over placebo [56]. Trospium 20 mg twice daily offered comparable efficacy and a better benefit:risk ratio compared with oxybutynin 5 mg twice daily in a European study of subjects with OAB due to its improved tolerability profile [57]. In this study, participants received continuous therapy with either trospium or oxybutynin for 52 weeks. Urodynamic assessments were carried out at baseline and weeks 26 and 52. In addition, subjects completed 7-day bladder diaries at baseline and during weeks 2, 26 and 52 to capture changes in micturition frequency, incontinence frequency, and the number of urgency episodes per day. Participants treated with trospium and oxybutynin experienced significant and

Table 3. Summary of two placebo-controlled, US-based clinical studies conducted among adults with OAB treated with trospium 20 mg twice daily.

Study	Study population	Design	Treatments	End points	Key findings	Ref.
Zinner *et al.* (2004)	n = 523 Adults ≥ 18 years with OAB of ≥ 6 months duration	12-week, multicenter, placebo-controlled trial	Trospium 20 mg b.i.d (n = 262) Placebo (n = 261)	Change in average number of toilet voids/day	Significant reduction in the number of toilet voids/day at weeks 1, 4 and 12 ($p \leq 0.05$ vs placebo)	[49]
				Change in average number of urge urinary incontinence episodes/day	Significant reduction in the number of urge urinary incontinence episodes/day at weeks 1, 4 and 12 ($p \leq 0.05$ vs placebo)	
				Safety and tolerability	Dry mouth and constipation were the two most commonly reported AEs considered at least possibly related to study treatment. AEs tended to occur early and to resolve with continuing treatment No clinically significant differences in vital signs, ECGs or laboratory values	
Rudy *et al.* (2006)	n = 658 Adults ≥ 18 years with OAB of ≥ 6 months duration	12-week, multicenter, placebo-controlled trial	Trospium 20 mg b.i.d (n = 329) Placebo (n = 329)	Change in average number of toilet voids/day	Significant reduction in the number of toilet voids/day at weeks 1, 4, and 12 ($p \leq 0.05$ vs placebo)	[50]
				Change in average number of urge urinary incontinence episodes/day and week	Significant reduction in the number of urge urinary incontinence episodes/day and week at weeks 1, 4 and 12 ($p \leq 0.05$ vs placebo)	
				Safety and tolerability	Dry mouth and constipation were the two most commonly reported AEs considered at least possibly related to study treatment No clinically significant differences in vital signs, ECGs or laboratory values	

AE: Adverse event; b.i.d: Twice daily; ECG: Electrocardiogram; OAB: Overactive bladder.

comparable increases in their mean maximum cystometric bladder capacity over the 52 weeks of treatment (an increase of 115 ml with trospium vs 119 ml with oxybutynin). Both treatment arms also reported relevant and comparable reductions in micturition frequency, incontinence frequency, and the number of urgency episodes/day.

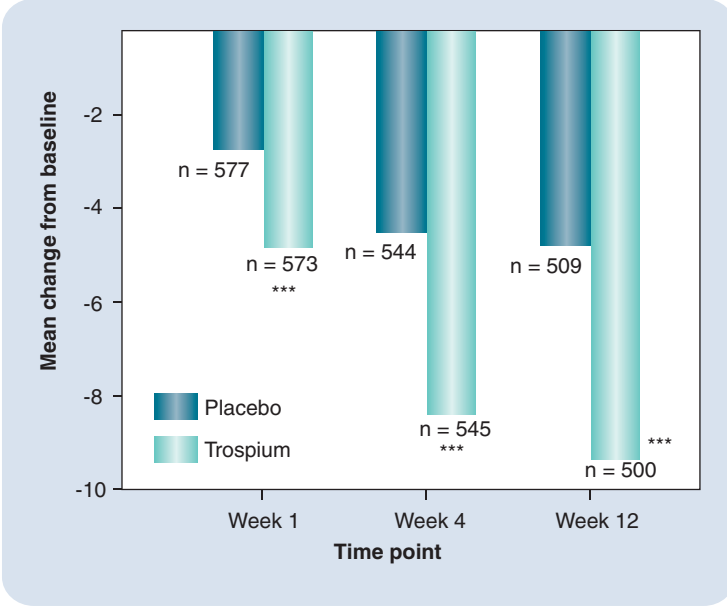
Safety & tolerability

Safety & tolerability of trospium versus placebo

The safety and tolerability of trospium have been assessed in a double-blind, placebo-controlled dose-finding study among 29 healthy adult male volunteers [35]. Subjects received single oral doses of trospium 20, 40, 80, 120, 180, 240 and 360 mg or placebo. Anticholinergic effects, including dilation of the pupils, dry mouth and increased heart rate, were reported with increasing severity for doses above 180 mg. However, even the maximum dose used in this study (360 mg) did not cause any relevant changes in vital signs, including blood pressure, pulse and electrocardiogram. As such, it would seem that doses well in excess of the current therapeutic daily dose of trospium (40 mg) are well tolerated [35].

The salutary tolerability of trospium has also been observed in the clinical trial setting

Figure 4. Mean change from baseline in Overactive Bladder Symptom Composite Score.



Mean change from baseline in Overactive Bladder (OAB)-Symptom Composite Score (SCS) among adults with OAB randomized to receive trospium 20 mg twice daily or placebo for up to 12 weeks (observed cases analysis) [53].
***p value < 0.0001 for treatment comparability from analysis of variance.

(**Tables 3 & 4**). In the two US-based, Phase III studies, trospium was generally well tolerated; dry mouth and constipation were the most commonly reported adverse events overall, with 20.1% of subjects treated with trospium 20 mg twice daily reporting dry mouth compared with 5.8% of subjects who received placebo [49,50,101]. Constipation was reported by 9.6% of trospium-treated subjects compared with 4.6% in the placebo group. The tolerability of trospium in these studies was also maintained for an extension period during which subjects who took part in one of the studies [49] were given the option of continuing with, or switching to, trospium for a further 9 months [52]. Dry mouth (11.3%) and constipation (8.8%) remained the most commonly reported adverse events during the extension phase [52].

In the European placebo-controlled studies, trospium 20 mg twice daily was also well tolerated (**Table 4**) [54,55]. Gastrointestinal disorders were the most commonly reported adverse events among all participants (trospium: 6.2%; placebo: 1.0%); dry mouth constituted almost half of these adverse events [54]. Among the 208 adults who took part in the second study, the overall frequency of adverse events was comparable between those treated with trospium (68%) and those who received placebo (62%). Again, the most frequently reported adverse event was dry mouth, reported by 43 subjects treated with trospium and 18 subjects who received placebo. All adverse events were transient and reversible and the majority of participants in both treatment arms assessed the acceptability of their study medication as good or very good (trospium 50 and 37%, respectively; placebo 40 and 29%, respectively [55]).

Safety & tolerability versus active comparators

The overall incidence of treatment-related adverse events was similar among subjects treated with trospium and those treated with tolterodine (34 and 32%, respectively) [56]. Adverse events were mostly mild in intensity in both treatment arms, with the most commonly reported adverse events being disturbances of the gastrointestinal tract. In the comparison with oxybutynin described above [57], 64.8% of subjects treated with trospium reported at least one adverse event compared with 76.7% of those treated with oxybutynin. The most commonly reported adverse event in both treatment arms was dry mouth. The weekly risk of experiencing dry mouth was 0.009 in those receiving trospium compared with 0.021 for oxybutynin [57].

CNS safety

The effects of trospium on daytime sleepiness and sleep architecture in healthy volunteers and adult subjects with OAB have been reported. In a subanalysis of the US-based Phase III study described previously [50], adults with OAB completed the Stanford Sleepiness Scale at weeks 1, 4 and 12 during treatment with trospium 20 mg twice daily or placebo. Those treated with trospium did not report any relevant increase in daytime sleepiness during the study period. A further analysis was conducted among subjects aged less than 65 years, 65 years or older, less than 75 years, and those aged 75 years or older. Again, no appreciable age-related effect on daytime sleepiness was revealed during treatment with trospium.

In a further, single-dose, placebo- and active comparator-controlled study among healthy volunteers aged 50 years or older, duration and latency of rapid eye movement (REM) sleep following a single oral dose of trospium was comparable to that of individuals who received placebo [59]. Reductions in REM sleep of approximately 15% were detected among adults who received single oral doses of oxybutynin or tolterodine; however, these changes were not

Table 4. Summary of European clinical studies conducted among adults with overactive bladder treated with trospium 20 mg twice daily .

Study	Study population	Design	Treatments	End points	Key findings	Ref.
Placebo-controlled						
Alloussi *et al.* (1998)	n = 309 Adults > 18 years with urge syndrome	3-week, multicenter, placebo-controlled trial	Trospium 20 mg b.i.d (n = 210) Placebo (n = 99)	Maximum cystometric bladder capacity	Significant increase in maximum bladder capacity (p = 0.0001 vs placebo; per-protocol analysis)	[54]
				Volume at first unstable contraction	More pronounced increased in volume at first unstable contraction (p = 0.0027 vs placebo)	
				Safety and tolerability	Gastrointestinal complaints, including dry mouth, were the most frequently reported AEs (6.2% of subjects treated with trospium chloride vs 1.0% of those who received placebo)	
Cardozo *et al.* (2000)	n = 208 Adults 18–70 years with urodynamically confirmed detrusor instability	3-week, multicenter, placebo-controlled trial	Trospium 20 mg b.i.d (n = 104) Placebo (n = 104)	Maximum cystometric bladder capacity	Significant increase in maximum cystometric bladder capacity ($p \leq 0.05$ vs placebo)	[55]
				Volume at first unstable contraction	Significant increase in volume at first unstable contraction ($p \leq 0.05$ vs placebo)	
				Safety and tolerability	Dry mouth and gastrointestinal disorders (abdominal pain, dyspepsia, nausea) were the most frequently reported AEs. All were transient and reversible	
Active comparator-controlled						
Junemann *et al.* (2000)	n = 232 Subjects with a medical history of pollakiuria >10/day, nocturia, and imperative desire to void	3-week, multicenter, placebo- and active comparator-controlled trial	Trospium 20 mg b.i.d, tolterodine 2 mg b.i.d, placebo	Change from baseline in daily micturition frequency	Trospium reduced micturition frequency compared with placebo	[56]

Table 4. Summary of European clinical studies conducted among adults with overactive bladder treated with trospium 20 mg twice daily (cont.).

				Safety and tolerability	Comparable overall incidence of treatment-related AEs with trospium (34%) and tolterodine (32%) compared with 15% for placebo. AEs were mostly mild gastrointestinal disturbances	
Halaska *et al.* (2003)	n = 358 Subjects with urge syndrome (undue frequency of micturition, nocturia, overwhelming urge, wetting) or urge urinary incontinence	52-week, multicenter, active comparator-controlled trial	Trospium 20 mg b.i.d Oxybutynin 5 mg b.i.d	Maximum cystometric bladder capacity. Volume at first uninhibited detrusor contraction. Volume at first sensation to void. Volume at maximum unstable detrusor contraction. Maximum detrusor pressure at first unstable contraction. Residual urine and maximum urinary flow rate.	No significant difference between trospium chloride and oxybutynin at 52 weeks in: – maximum cystometric bladder capacity – volume at first unstable contraction – volume at first sensation to void – decrease from baseline in micturition frequency and urgency episodes	[57]
				Safety and tolerability	Lower overall incidence of AEs with trospium chloride (48%) compared with oxybutynin (59%), including fewer gastrointestinal AEs (39 vs 51%, respectively) and less dry mouth (33 vs 50%, respectively)	

AE: Adverse event; b.i.d: Twice daily.

regarded to have reached a pathological degree, and as such, impairment in concentration or cognitive function would not be expected.

The potential effects of trospium on other measures of CNS functioning have also been reported. In a Phase I comparison with oxybutynin among 12 healthy volunteers, multichannel EEG revealed significant decreases in α and β_1 activity following administration of oxybutynin [32]. No such effects were noticed following either intravenous or oral administration of trospium [32]. The results of this preliminary study were confirmed in a placebo-controlled, single-blind comparison of oxybutynin, tolterodine and trospium [34]. Subjects received either placebo or the recommended dose of each agent in three divided doses over the course of a single day and underwent quantitative EEG assessment before and for up to 4 h after each dose. Neither trospium nor tolterodine effected any changes in five of the six frequency bands assessed. However, oxybutynin was associated with significant changes in four of the six frequency bands [34].

Postmarketing surveillance

Since trospium first became available in Europe for the treatment of OAB, over 110 million patient-days of therapy have been accumulated. Results across six major European postmarketing surveillance studies confirmed the results of the controlled

Highlights

- Trospium, an antimuscarinic agent with an unusual quaternary amine structure, has recently become available in the USA for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence (UUI), urgency and urinary frequency. The availability of trospium in Europe for over 20 years has resulted in a wealth of information regarding its safety and efficacy, including postmarketing experience from more than 110 million patient days of therapy.
- Clinical trials indicate that treatment with trospium significantly decreases the average frequency of toilet voids and UUI episodes, significantly increases average volume per void and decreases daytime frequency compared with placebo. In addition to these standard measures by which efficacy in treating OAB is evaluated, treatment with trospium results in significant reductions in patient-reported urgency.
- As a quaternary amine, trospium has pharmacological properties that are distinct from other antimuscarinic agents available and which contribute to its salutary safety and efficacy profile.
  – Low lipophilicity and ionization at a neutral pH limit the ability of trospium to cross the blood–brain barrier and cause centrally mediated adverse events. Lack of penetration into the CNS is also supported by clinical evidence, including both electroencephalograph and sleep studies.
  – Metabolism independent of the cytochrome P450 isoenzyme system allows confident prescription of trospium alongside the majority of commonly used drugs without fear of adverse drug–drug interactions.
- The presence of unchanged trospium in the bladder – its primary therapeutic site of action – may contribute to the pharmacological activity of the agent, providing earlier onset and improved and prolonged efficacy compared with other, more extensively metabolized antimuscarinic agents.

clinical trials, with improvements in micturition frequency, nocturia, urgency and UUI. Subjects also reported reductions in their use of incontinence aids and improvement in their overall QoL [60]. Among the 10,759 subjects who took part in these postmarketing surveillance studies, 5.1% reported adverse events. Dry mouth remained the single most frequently reported adverse event and was experienced by 4.1% of subjects [60].

Expert commentary & outlook

Trospium chloride, a positively-charged quaternary amine, has pharmacological properties that distinguish it from other antimuscarinic agents available for the treatment of OAB, all of which are tertiary amines. The pharmacological properties of trospium translate into a wealth of benefits, including a reduced likelihood of drug–drug interactions with commonly prescribed agents, a low propensity for CNS adverse events, and the potential to provide local inhibitory effects via the urothelium. All of these benefits contribute to the salutary safety and efficacy profile of this agent. A once-daily formulation of trospium is currently in clinical trials and, if approved, will be a valuable addition to the current selection of OAB therapies, as the only once-daily quaternary amine.

In addition to trospium and the five other branded products on the market today, fesoterodine (the metabolite of tolterodine) has been shown to be more effective than placebo in randomized controlled trials. It is currently being prepared for US FDA submission. SVT-40776 is a new M_3-specific anticholinergic agent currently in Phase II clinical trials. While potassium channel openers and neurokinin-1 inhibitors have been tested unsuccessfully for OAB symptoms in the past, nociceptin orphan peptide agonists may be a new class of drugs for the treatment of OAB. These exert their effect by activating the nociceptin orphan peptide receptor to inhibit the micturition reflex. Early work with selective prostaglandin inhibitors and purinergic receptor blockers indicates that they may also be the source of effective OAB treatments in the future.

In the years ahead we are likely to see alternative delivery systems for anticholinergic agents, such as through the skin and intravesically. Intravesical delivery of vanilloids, such as capsaicin and resiniferatoxin has been disappointing, but other drugs targeted at urothelial muscarinic receptors may offer promise in the future for treatment of detrusor overactivity and OAB. Transurethral botulinum toxin injections have shown good efficacy for treatment of both neurogenic and idiopathic detrusor overactivity in subjects who have failed anticholinergic treatment. Whether this will be a viable long-term treatment of detrusor overactivity is unclear.

Improvements in neuromodulation and peripheral nerve stimulation may also improve the management of OAB in the future. Early research with newer stimulators implanted along the pudendal nerve or periurethrally shows that they may be more effective at blocking the afferent arc of the micturition reflex than central sacral nerve stimulation. These devices may also be effective in the treatment of painful bladder disorders. The good news for our patients is that now, more than ever before, expanded research efforts are being made into the treatment and etiology of OAB.

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Website

101. Esprit Pharma and Indevus Pharmaceuticals Inc. Sanctura™ prescribing information. www.sanctura.com.

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