REVIEW ARTICLE

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Safety and Tolerability Profiles of Anticholinergic Agents Used for the Treatment of Overactive Bladder

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Contents

Abstract . . . 733
1. Literature Search Methodology . . . 735
2. Mechanism of Action of Anticholinergics . . . 735
3. Pharmacological Profile . . . 736
4. Muscarinic Receptor Binding . . . 736
   4.1 Pharmacokinetics . . . 737
   4.2 Different Formulations . . . 737
   4.3 Drug-Drug Interactions . . . 738
5. CNS and Cardiac Safety Issues with Anticholinergics . . . 739
   5.1 Access to the CNS . . . 739
   5.2 CNS Events . . . 739
   5.3 Cardiac Events . . . 741
6. Common Adverse Events of Anticholinergics . . . 741
   6.1 Dry Mouth . . . 742
      6.1.1 Data from Randomized Controlled Trials (RCTs) with Long-Acting Formulations . . . 742
      6.1.2 Comparative Data . . . 745
   6.2 Constipation . . . 746
      6.2.1 Data from RCTs with Long-Acting Formulations . . . 746
      6.2.2 Comparative Data . . . 746
   6.3 Headache . . . 746
      6.3.1 Data from RCTs with Long-Acting Formulations . . . 747
      6.3.2 Comparative Data . . . 747
   6.4 Blurred/Abnormal Vision . . . 747
      6.4.1 Data from RCTs with Long-Acting Formulations . . . 747
      6.4.2 Comparative Data . . . 747
   6.5 Dyspepsia . . . 747
      6.5.1 Comparative Data . . . 747
7. Adverse Effects and Treatment Adherence . . . 747
8. Impact of Trial Design on Adverse Event Rates . . . 748
9. Conclusions . . . 749

Abstract

Anticholinergics are the mainstay of pharmacotherapy for overactive bladder (OAB). The anticholinergics used to treat OAB differ in their pharmacological profiles, which may affect their propensity for causing commonly observed adverse effects. The purpose of this is review is to use published

clinical data to evaluate the safety and tolerability of commonly prescribed anticholinergics for OAB, provide a context for safety and tolerability in terms of drug pharmacology, summarize the impact of adverse effects on adherence, and discuss the influence of study design on safety and tolerability outcomes. A MEDLINE search was conducted for the period 1990–2010 to identify studies evaluating mechanisms of action, pharmacological profiles, safety issues and adverse events pertaining to anticholinergics used in the treatment of OAB.

Compared with immediate-release preparations, the extended-release, once daily and transdermal formulations are associated with lower rates of anticholinergic adverse effects, due to improved consistency in serum levels. The most significant adverse effects in terms of affecting the use of anticholinergics agents are CNS and cardiac disturbances. CNS issues are associated with pharmacological properties such as serum concentration, blood-brain barrier permeability and active transport, and receptor binding affinity. Cardiac safety (corrected QT interval) is more dependent on specific molecular attributes. However, more common but less bothersome adverse effects associated with systemic blockade of the muscarinic receptors include dry mouth, constipation, headache and blurred vision. A high potential for interaction between anticholinergics and drugs that compete with the same pathways for hepatic metabolism via cytochrome P450 and renal excretion increases the risk of adverse effects for both antimuscarinic and associated medications, especially in the elderly, who are more likely to be taking multiple drugs.

This literature review demonstrates that all OAB anticholinergics are effective in reducing symptoms of OAB; however, important pharmacodynamic/pharmacokinetic differences between these agents may influence their efficacy and incidence of associated adverse effects. Because OAB is a chronic disease requiring long-term therapy, careful assessment of the pharmacological differences is needed in order to tailor therapy to the individual patient's clinical needs, and thereby maximize the chance of treatment success and long-term adherence to therapy. Since anticholinergic adverse effects are known to affect treatment adherence and persistence, the potential for adverse effects should be considered when selecting treatment for an individual patient.

Overactive bladder (OAB) is a common disorder affecting approximately 33 million adults in the US, with prevalence increasing with age.[1,2] Anticholinergic (antimuscarinic) agents are the most widely used and preferred first-line pharmacological options for OAB. The available anticholinergic agents and their active metabolites differ in their pharmacological profiles, which may influence their propensity for causing the adverse effects commonly noted in clinical practice.[3] The drug formulation is also relevant, with extended-release (ER), once daily and transdermal formulations causing fewer anticholinergic adverse effects due to improved consistency in concentrations, compared with immediate-release (IR) preparations with higher peak plasma concentrations.[4,5]

Clinicians should also be aware of the high potential for drug-drug interactions (DDIs) between anticholinergics metabolized by the cytochrome P450 (CYP) system and drugs that compete with the same pathways for hepatic metabolism or renal excretion.[6] Such interactions increase the risk of adverse effects; this is especially important among the elderly, who are more likely to be taking multiple drugs for a range of conditions, and in patients receiving maximal doses.[6]

In view of the distribution of muscarinic receptors in various organs throughout the body,

anticholinergics may be associated with adverse effects such as dry mouth, constipation, dizziness and CNS-associated adverse effects.[7,8] The most serious safety issues in terms of affecting the use of anticholinergics agents are CNS or cardiac disturbances.[3,9] The risk of CNS issues, such as headache, somnolence and cognitive deficits, is dependent on a combination of pharmacological properties such as absorption rates, metabolism, serum concentration, blood-brain barrier (BBB) permeability, ability to be actively transported across the BBB (P-glycoprotein substrate) and receptor binding affinity.[7] By comparison, cardiac safety (particularly corrected QT interval [QT_c] prolongation) is dependent mainly on specific muscarinic receptor binding affinity.[9] The more common, but usually less bothersome, adverse effects associated with systemic blockade of muscarinic receptors include dry mouth (salivary glands), constipation (colon) and blurred vision (eyes). Since anticholinergic adverse effects are known to affect adherence and are a common cause of treatment discontinuation, the adverse effect profile should be considered when selecting treatment for an individual patient.[10]

This article uses clinical data to review the safety and tolerability of commonly prescribed anticholinergics for OAB, provides a context for safety and tolerability in terms of drug pharmacology (mechanism of action, receptor affinity, formulation and pharmacokinetics), summarizes the impact of adverse effects on adherence and discusses the influence of study design on safety and tolerability outcomes.

1. Literature Search Methodology

A MEDLINE search was conducted for the time period 1990–2010 to identify English-language studies evaluating, and other information relevant to, mechanisms of action, pharmacological profiles, safety issues and adverse events pertaining to antimuscarinics used in the treatment of OAB. Additional studies were identified from the US prescribing information for these drugs, and reference lists of published articles identified in searches. Key search terms included 'anticholinergic', 'antimuscarinic', 'darifenacin', 'fesoterodine', 'oxybutynin', 'solifenacin', 'tolterodine', 'trospium', 'overactive bladder', 'incontinence', 'efficacy', 'safety', 'adverse event', 'central nervous system', 'cardiac', 'receptor', 'pharmacokinetic', 'formulation' and 'drug-drug interaction'.

2. Mechanism of Action of Anticholinergics

Anticholinergic agents antagonize the muscarinic receptors. The afferent effect of anticholinergic agents on the bladder, exerted via motor and sensory pathways, is both muscular and urothelial in nature. Action on the motor pathway blocks a facilitatory mechanism (the inhibition of accommodation and contractility), thereby antagonizing post-junctional excitatory muscarinic acetylcholine receptors in the detrusor muscle, and competing with the parasympathetic acetylcholine pathway. Action via the sensory pathway allows the anticholinergic agent to modulate afferent innervations in the urothelium, thereby altering sensory feedback during filling.[11]

A potential secondary mechanism of action has been proposed whereby antimuscarinics exhibit a direct local effect on muscarinic receptors (M_2) in the urothelium, in addition to the indirect effect brought about by the sensory nerve pathways. Evidence for this local effect is drawn from studies investigating the direct intravesical instillation of drug (oxybutynin or trospium chloride) into the bladder,[12-15] as well as studies of orally administered drugs (solifenacin or trospium chloride) renally excreted as active parent drug or metabolite in human urine and then instilled into the bladder of animal OAB models.[16,17]

Of note, the bladder has an efficient natural barrier against resorption of substances in urine, particularly electrolytes such as potassium, that could affect polarization of detrusor smooth muscle cells.[18] The 'blood-bladder' barrier may be equated with the BBB with respect to passage of relatively small, lipophilic molecules that are not actively transported. Data from studies using intravesical administration of anticholinergic agents indicate that trospium chloride is not absorbed into the circulation in significant amounts,[13,15] whereas intravesical oxybutynin is readily absorbed

and its elimination is prolonged compared with oral administration;[14] however, intravesical oxybutynin is associated with fewer systemic anticholinergic adverse events than oral oxybutynin.

3. Pharmacological Profile

An important influence on the safety and tolerability of the OAB anticholinergic agents are their pharmacological profiles (table I).[19-27]

4. Muscarinic Receptor Binding

Muscarinic receptors are present in the bladder and other organs, including the salivary glands, gut, eyes and brain (table II).[32] In the bladder, approximately 80–90% of muscarinic receptors are of the M_2 subtype and 10–20% are M_3. By comparison, the colon contains 90% M_3 and 10% M_2 receptors.

Agents differ in their affinity for the muscarinic receptor subtypes.[33] Most data on receptor subtype affinity come from animal models and *in vitro* experiments. From these studies, it appears that tolterodine, fesoterodine and trospium chloride are 'balanced' with respect to their affinity for the five muscarinic receptor subtypes.[3,28] Of note, darifenacin is most selective for the M_3 subtype and least selective for M_4 and M_2. Similarly, solifenacin and oxybutynin have greater selectivity for M_3 and M_1 than M_2.[3] The differing patterns of subtype selectivity appear to influence the type and severity of adverse effects associated with these agents, but not their efficacy.[33] For example, the ratio of binding affinity for $M_3 : M_1$ subtypes is greatest for darifenacin, with trospium, oxybutynin and tolterodine being equipotent for M_3 and M_1 subtypes. Antimuscarinic agents with similar M_3 and M_1 affinity, such as oxybutynin and tolterodine, have the greatest risk of adverse CNS effects, whereas M_3-selective agents darifenacin and solifenacin have a lower risk of CNS effects. Although trospium is equipotent for M_3 and M_1 receptors, it does not cause CNS effects by virtue of not being able to penetrate the BBB.

Table I. Pharmacological profiles of the anticholinergic agents available in the US[3,19-31] (adapted from Abrams and Andersson,[3] with permission from John Wiley and Sons)

Parameter	Oxybutynin IR/ER	Oxybutynin TDS/OTG	Tolterodine IR/ER	Trospium chloride IR/ER	Darifenacin	Solifenacin	Fesoterodine
Molecular weight	393.9	357/393.9	475.6	428	507.5	480.6	527.7
Octanol : water coefficient at pH 7.4[a]	>3.30	>3.30[b]	1.83	−1.22	NA (highly lipophilic)	1.69	0.47 (5-HMT)
Polarity (at 9.20 pKa)	Neutral	Neutral[b]	Positive	Highly positive	Positive	Positive	NA
Metabolizing enzymes	CYP3A4	CYP3A4[b]	CYP2D6, CYP3A4	Ester hydrolysis by non-CYP enzymes	CYP2D6, CYP3A4	CYP3A4	Hydrolysis of fesoterodine (prodrug) by plasma esterases to 5-HMT, CYP2D6, CYP3A4 (5-HMT)
Half-life (h)	2/13	7–8/NA	2/8	19/36	12	45–68	7.3–8.6

a Numbers >0 indicate lipophilic; the larger the number, the more lipophilic the molecule.

b Data same as for oxybutynin TDS.

5-HMT = 5-hydroxymethyl tolterodine; **CYP** = cytochrome P450; **ER** = extended-release; **IR** = immediate-release; **NA** = not available; **OTG** = oxybutynin chloride topical gel; **TDS** = transdermal delivery system.

Table II. Functionally important muscarinic receptor subtypes in different tissues[32]

Tissue	Receptor subtype
Bladder	M_3, M_2
Salivary glands	M_3, M_1
Gastrointestinal tract	M_3, M_2
Eye	M_2, M_3, M_5
Heart	M_2
Brain cortex (cognitive processing)	M_1, M_2

Data suggest that the overall efficacy/adverse event profile is related to the $M_2:M_3$ binding affinity ratio (figure 1). Given the high proportion of M_3 receptors in the colon and salivary glands, a low $M_2:M_3$ ratio such as seen with darifenacin and solifenacin is associated with a greater propensity to cause constipation and dry mouth than agents with a higher $M_2:M_3$ ratio. Tolterodine, which demonstrates relatively equipotent selectivity for M_2 and M_3 receptors, has been shown to have functional selectivity for the bladder over the salivary glands and a significantly lower incidence of dry mouth compared with the relatively M_3-selective antimuscarinic oxybutynin.[36] The lower M_2 binding affinity with darifenacin appears to confer a lower risk of cardiac effects than a higher M_2 selectivity as seen with tolterodine.[33,37] The generation and subsequent binding of active metabolites to muscarinic receptors can also play a role in safety and tolerability. For example, oxybutynin is extensively metabolized to the active metabolite N-desethyloxybutynin, which has a worse adverse event profile compared with its parent compound, and increased serum concentrations of this metabolite appear to be related to an increased incidence of anticholinergic adverse effects (see section 4.1).[38]

4.1 Pharmacokinetics

Most of the OAB anticholinergics, with the exception of trospium chloride, have active metabolites that contribute to their clinical effect. Oral oxybutynin, tolterodine, solifenacin and darifenacin are extensively metabolized by the CYP isoenzymes in the liver, principally CYP3A4 for oxybutynin and solifenacin, and CYP3A4 and CYP2D6 for darifenacin and tolterodine, respectively.[3,20-22,24,39] Fesoterodine, a prodrug, is converted by a serum esterase to its active metabolite 5-hydroxymethyl tolterodine (5-HMT), which is then metabolized in the liver by CYP3A4 and CYP2D6 into inactive metabolites.[26,28] In contrast, trospium chloride is metabolized by a ubiquitous hepatic esterase (non-CYP pathway), and no active metabolites are produced (table III).[19]

Oxybutynin is metabolized to N-desethyloxybutynin, which has similar activity to the parent compound but is believed to have a greater binding affinity for muscarinic receptors in the salivary gland than in the bladder.[38] Serum concentrations of the metabolite are 5- to 11-fold higher than the parent compound after administration of oxybutynin IR, but are about one-third lower than oxybutynin concentrations after administration of the ER formulation, and one-tenth lower than with transdermal delivery. This has been proposed as a reason for the lower rate of dry mouth with the transdermal or ER formulations versus the IR formulation.[38]

4.2 Different Formulations

A number of the anticholinergic agents have short half-lives and need to be administered more than once daily, and up to four times daily (for oxybutynin IR). Therefore, ER formulations have

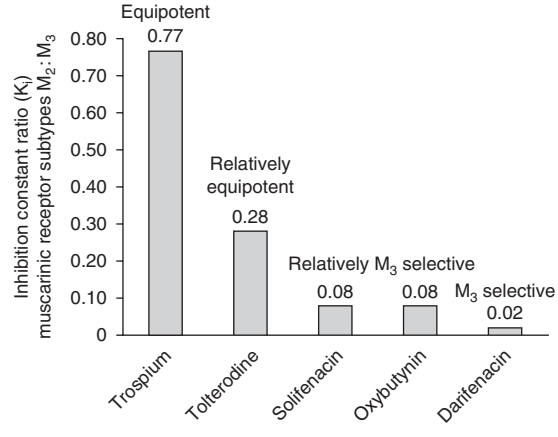

Fig. 1. Muscarinic receptor selectivity: $M_2:M_3$ ratio.[34,35]

Table III. Active parent anticholinergic agents and their active metabolites

Drug	Active parent	Active metabolite
Trospium	Yes	No
Darifenacin	Yes	Yes (minor)
Tolterodine	Yes	Yes (major; 5-HMT: better profile than parent)
Solifenacin	Yes	Yes (minor)
Oxybutynin	Yes	Yes (major; N-DEO; worse profile than parent)
Fesoterodine	No	Yes (major; 5-HMT)

5-HMT = 5-hydroxymethyl tolterodine; **N-DEO** = N-desethyloxybutynin.

been developed. These formulations are associated with a reduced incidence of adverse effects, attributed to lower peak drug concentrations, whereas a slow constant release of the drug, which reduces the peak and trough effect, results in better symptom control.[8] The controlled-release, oral formulation of oxybutynin uses osmotic pressure to release the drug slowly: through a semi-permeable membrane for the branded XL formulation, and a wax matrix for the generic ER formulation. The ER preparation of tolterodine uses membrane-coated, slow-release beads in a gelatin capsule. The release of tolterodine from the ER formulation is pH dependent, whereas release of oxybutynin from the ER tablet is not; therefore, tolterodine ER release is greater in the presence of antacids.[40] Among the newer anticholinergic agents, both darifenacin and fesoterodine are available only as ER formulations (no IR formulations were developed for clinical use) using a matrix tablet preparation. Solifenacin is the only OAB anticholinergic with a sufficiently long half-life, allowing it to be administered once daily. Trospium chloride is available in both IR and ER formulations; the ER formulation uses a time- and pH-dependent release technology to maximize drug release in the upper gastrointestinal tract and must be taken on an empty stomach.

4.3 Drug-Drug Interactions

A number of conditions can be commonly co-morbid with OAB and since the prevalence of OAB increases with age, older patients may be likely to have additional co-morbidities requiring treatment. The more concurrent medications a patient takes, the more likely that a DDI can occur.[41,42] One of the ways in which a DDI can occur is when two or more drugs interact to increase or decrease the drug concentration, which can increase or decrease the adverse effects reported.[6] Although few DDIs have been reported and studied with anticholinergic agents, they have the potential to interfere with medications commonly prescribed in patients with OAB. For example, there have been several case reports of increased international normalized ratios following the addition of tolterodine in patients previously stable on warfarin therapy,[43,44] although a study in healthy volunteers indicated that there was no pharmacokinetic or pharmacodynamic effect of tolterodine on single-dose warfarin.[45]

The tertiary amine anticholinergics used to treat OAB are metabolized by the hepatic CYP enzyme pathway (table I), primarily by CYP3A4 and CYP2D6, and therefore there is the potential for DDIs with the many other drugs metabolized via this pathway. The CYP isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 are responsible for the metabolism of 90% of drugs, with 3A4 (50%) and 2D6 (25%) accounting for 75%.[46] For example, administration of the potent CYP2D6 inhibitor fluoxetine inhibits the metabolism of tolterodine, although changes in exposure to the active moiety (unbound tolterodine plus the active metabolite 5-HMT) are considered to be within normal variation.[47] Similarly, darifenacin exposure is increased by 33% with coadministration of the potent CYP2D6 inhibitor paroxetine.[21,48] No dosing adjustments are recommended as a result of these DDIs.[21,24,25] Potent inhibitors of CYP3A4 such as ketoconazole can similarly inhibit metabolism via CYP3A4, as seen with darifenacin,[49] fesoterodine (with regard to the active metabolite 5-HMT derived from the prodrug),[50] oxybutynin,[51] solifenacin[52] and tolterodine,[53] necessitating caution (oxybutynin) or use of a lower dose (darifenacin, fesoterodine, solifenacin and tolterodine) for patients concomitantly receiving potent CYP3A4 inhibitors.[20-26]

Unlike the other OAB anticholinergic agents, the quaternary amine anticholinergic trospium chloride is not metabolized by the CYP system,

but is renally eliminated, largely unchanged.[54] Renal elimination has the potential for DDIs via competition for renal excretion; however, recent evidence indicates that the renally eliminated drugs digoxin and metformin are safe when coadministered with trospium chloride.[55,56]

5. CNS and Cardiac Safety Issues with Anticholinergics

5.1 Access to the CNS

The distribution of a drug in the body and its ability to access specific parts of the body such as the brain may also contribute to the likelihood of adverse effects.[8] The hydrophilic or lipophilic nature, polarity and molecular size of an agent are the main factors that affect the incidence of CNS-associated adverse effects. Only small, non-polarized, lipid-soluble molecules are expected to be able to cross the BBB.[57] Apart from trospium chloride, all the OAB anticholinergics are lipophilic, with the potential of crossing the BBB and resulting in CNS adverse effects.[8] For example, at physiological pH (7.4), all anticholinergics except trospium chloride have an octanol : water coefficient (logD) >0 (table I), indicating lipophilicity,[29] which permits crossing the BBB. The active metabolite of tolterodine and fesoterodine (5-HMT) has the next lowest lipophilicity with a logD of 0.47.[29] In contrast, trospium chloride is hydrophilic (logD −1.22).[8]

The polarity of the anticholinergics is listed in table I. The IR, ER and transdermal delivery system (TDS) formulations of oxybutynin are neutral at physiological pH, whereas tolterodine IR and ER and darifenacin are positively charged (a higher pK_a value [negative logarithm of acid ionization constant] correlates with easier BBB penetration).[58] Trospium chloride is always positively charged at physiological pH and ionized across the entire pH range,[8] and solifenacin is 93% positively charged at pH 7.4.[30] The polarity of 5-HMT at physiological pH is not known. Smaller molecules will be able to penetrate the pores in the BBB. The size of the active parent or metabolite ranked from largest to smallest is darifenacin > solifenacin > tolterodine > trospium chloride > fesoterodine > oxybutynin.

Given its hydrophilicity, positive charge and larger molecular size, trospium chloride is not expected to cross the BBB, thereby reducing its propensity for CNS and cognitive adverse effects.[8] This prediction was recently confirmed in a study that showed that elderly human subjects with OAB did not have assay-detectable concentrations of trospium chloride in the cerebrospinal fluid despite peak plasma steady-state levels.[59,60] In addition, no pre- or post-dose change in memory was identified in this cohort.

Ability to be removed from the CNS by active transport across the BBB is also relevant to the propensity of the OAB anticholinergics to cause CNS adverse effects. Studies have shown trospium chloride (*in vivo*) and darifenacin and fesoterodine (*in vitro*) to be substrates of the drug efflux pump P-glycoprotein, unlike oxybutynin.[61-64]

5.2 CNS Events

Adverse CNS events expected with some OAB anticholinergics and reported in clinical trials include somnolence, dizziness, depression, cognitive impairment, psychosis, EEG changes, sleep deficits, hallucinations, confusion and behavioural disturbances. Somnolence appears to be less of a problem with oxybutynin TDS, solifenacin, darifenacin, trospium chloride and fesoterodine, as it is not reported in prescribing information, presumably because the incidence was below the threshold of 1%.

In the meta-analysis by Chapple et al.,[65] there was no significant difference between any of the OAB anticholinergics in the incidence of CNS adverse events. However, differences between agents have been reported in some clinical trials. For example, there were no reports of dizziness with darifenacin 15 mg/day (maximum recommended dose) therapy, whereas 3% of oxybutynin IR recipients reported dizziness.[66] The incidence of dizziness was also slightly lower with tolterodine ER (1.7%) compared with oxybutynin IR (2.5%) in a Japanese study.[67] The opposite occurred in a comparison of tolterodine IR (8%) and oxybutynin IR (5%) in patients aged ≥50 years.[68]

Overall, the incidence of dizziness with tolterodine ER is between 0% and 5%.[67,69-74] Dizziness, somnolence, depression and confusion were infrequent in tolterodine ER and oxybutynin ER recipients in the OPERA (Overactive bladder: Performance of Extended Release Agents) trial.[75,76] The US prescribing information for oral oxybutynin was amended in 2008 to include the potential for anticholinergic CNS events and a warning to monitor patients for adverse CNS effects.[22,23]

However, the relatively low incidence of CNS adverse events in clinical trials of OAB anticholinergics may be partly because they used unsolicited CNS adverse event reporting, enrolled a heterogeneous population of patients with varying degrees of susceptibility and risk, and used methodologies that were underpowered to detect differences from placebo.[7] Thus, when cognitive performance of older volunteers was specifically evaluated, it was shown that cognitive performance measures were significantly impaired following oxybutynin ER, but not darifenacin therapy in placebo-controlled trials.[57,77,78] It is noteworthy that a recent study comparing the effects of oxybutynin on cognition in older patients (60–79 years of age) showed that the topical gel formulation of oxybutynin chloride had no significant effects on two tests of memory and other cognitive functions, compared with placebo, suggesting an association between route of administration and adverse effects on cognition.[79] In addition, a study by Lackner et al.[80] showed that short-term treatment (4 weeks) with oxybutynin ER 5 mg/day did not result in cognitive decline (as measured by the Confusion Assessment Method) or delirium in cognitively impaired (i.e. mild-to-severe dementia) elderly female nursing home residents.

In the open-label SMART (Sanctura Muscarinic Antagonist Resists Transport) trial, elderly subjects with OAB (n = 12; mean age 68 years) receiving trospium chloride ER 60 mg/day demonstrated no evidence of BBB penetration by the drug at day 10 steady state, and no changes in learning or memory as measured by the Hopkins Visual Learning Test-Revised.[59,60] Another study reported that elderly subjects (aged ≥65 years; mean age 79 years) with Alzheimer's disease and urge urinary incontinence who were receiving trospium chloride IR (45–60 mg/day) in combination with the cholinesterase inhibitor galantamine (up to 24 mg/day) for 6 months had no significant change in Mini-Mental State Examination scores.[81]

A small study (n = 9) in patients with Alzheimer's disease suggested that the use of OAB anticholinergics (in this case, tolterodine or oxybutynin) worsened cognitive function and behaviour, and did not meaningfully reduce incontinence episodes.[82] The changes in mental status correlated with changes in serum anticholinergic concentrations, suggesting a direct relationship between anticholinergic load and muscarinic-mediated processing in the CNS.[82]

The concept of anticholinergic load or burden may also be relevant in patients without underlying cognitive impairment,[83] particularly in the elderly.[84] A number of drugs from various classes have anticholinergic effects; these include antihistamines, anti-ulcer drugs, bronchodilators, cardiovascular drugs (ACE inhibitors, anticoagulants and calcium channel antagonists), muscle relaxants and specific CNS medications (antidepressants, antipsychotics, benzodiazepines and opioid analgesics).[85] The increased anticholinergic burden resulting from concomitant use of such medications can potentially increase the frequency of systemic adverse events.[83]

Certainly, pharmacodynamic studies in healthy volunteers seem to support a direct CNS effect of some anticholinergic agents. In one study, oxybutynin administration resulted in significant power reductions in EEG frequency bands (considered biomarkers for evaluating the impact of drugs on CNS functioning), whereas trospium chloride and tolterodine had no or minimal effects.[86]

Similarly, sleep architecture (as assessed by polysomnography) in healthy volunteers without sleep-related problems was influenced by some anticholinergics, with different effects in younger subjects (aged <36 years)[87] than older subjects (aged ≥50 years).[88] In younger subjects, rapid eye movement (REM) sleep duration (as a percentage of total sleep time) was significantly reduced after oxybutynin compared with trospium chloride (18.4% vs 20.2%; $p < 0.05$), although the reduction after oxybutynin compared with

placebo and tolterodine (20.1% and 19.1%, respectively) did not reach significance.[87] In contrast, both oxybutynin and tolterodine significantly reduced REM sleep compared with placebo in older subjects, but trospium chloride did not.[88] These studies suggest that, even with the potentially compromised BBB in older subjects, appreciable CNS changes are not seen with trospium chloride. In addition, a recent retrospective analysis of data from two randomized, double-blind, placebo-controlled trials found that in patients receiving tolterodine, REM sleep was decreased in CYP2D6-poor or -intermediate metabolizers, but not in extensive metabolizers.[89]

There have been reports of hallucinations, confusion and behavioural disturbances among elderly people receiving anticholinergics, particularly oxybutynin and tolterodine.[90-94] However, in the published review[91] of oxybutynin case reports, all of the patients had Parkinson's disease. Several patients also had pre-existing mild cognitive impairment, and severe dementia in one case, which may have put these patients at increased risk for the aforementioned adverse effects.[90] Prescription-event monitoring data from the UK found an incidence of hallucinations with tolterodine of 4.46 per 1000 patient-years of treatment. Patients who developed hallucinations were aged 70–92 years (median age 79 years).[92]

5.3 Cardiac Events

Because of the presence of muscarinic receptors in the heart, there is potential for anticholinergic agents to increase heart rate.[9] For example, trospium IR has been shown to result in a mean elevation in heart rate of 9 beats per minute (bpm) for the 20 mg dose versus placebo, while an extended release formulation of trospium elevated heart rate by approximately 3 bpm.[19] There is also an increased risk for prolongation of the QT interval and induction of polymorphic ventricular tachycardia (torsades de pointes), although QT prolongation and its consequences are not related to antimuscarinic activity, but are linked to inhibition of the human *ether-à-go-go*-related gene potassium channel in the heart.[95] However, clinical arrhythmias other than tachycardia are rarely reported with anticholinergics. True ventricular arrhythmia has been associated with QT_c prolongation. QT_c prolongation has been reported with tolterodine,[25] fesoterodine[26] and solifenacin in clinical trials,[20] and with solifenacin in postmarketing surveillance.[20]

The prescribing information for both oxybutynin IR and ER lists palpitations as occurring in ≥1% but <5% of patients.[22,23] The incidence of such events appears to be <1% of patients with the other OAB anticholinergics, based on prescribing information, although the prescribing information for tolterodine IR and ER, solifenacin and trospium chloride IR note that palpitations, tachycardia or cardiac rhythm disorders have been reported in postmarketing surveillance.[19,20,24]

Prescription-event monitoring data from the UK suggest that the incidence of palpitations/tachycardia with tolterodine may be approximately 8 per 1000 patient-years.[92] This was higher than the incidence estimated for terodiline (an older antimuscarinic agent) in the same analysis (risk with terodiline, 5.86 [95% CI 3.93, 8.75]). These events were as likely to occur in men as in women, and tended to be more likely in older than younger patients (based on the median age).[92]

Data from volunteers suggest that standard and supratherapeutic doses of tolterodine IR cause a modest, but not clinically relevant, increase in the QT interval of 1–12 msec.[96] As exposure to tolterodine is increased with concomitant administration of potent inhibitors of CYP2D6 or CYP3A4, such an increase could potentially increase the likelihood of adverse effects such as these if recommended dosage adjustments are not made. No changes in QT interval were seen in a study in volunteers receiving darifenacin at doses of 15–75 mg,[97] a study in elderly women with OAB receiving oxybutynin IR[98] or studies with trospium chloride at doses up to 180 mg.[9,99]

6. Common Adverse Events of Anticholinergics

The most common anticholinergic adverse effects of these agents include dry mouth, constipation, headache and blurred/abnormal vision. The incidences of these adverse events reported in random-

ized controlled trials (RCTs) with the once-daily preparations of OAB anticholinergics are summarized in table IV.[67,69-75,100-123,125-127,129,130]

Anticholinergics are also associated with other adverse events such as CNS effects (e.g. dizziness and somnolence), heartburn/dyspepsia and cardiac events (QT_c interval prolongation) [incidences summarized in table V]. In the clinical trial setting, most adverse events associated with OAB anticholinergics are mild to moderate and do not result in treatment discontinuation.

Although elderly patients may be at greater risk of adverse effects, data with tolterodine ER[73] suggest a similar incidence of adverse events in those aged ≥65 years as in younger patients, and data with darifenacin[110,131] and solifenacin[121] showed no increase in adverse events in those aged ≥65 years compared with data from studies in the overall OAB population. Data with trospium chloride ER indicate a similar incidence of adverse events in a subgroup of patients aged ≥75 years compared with the overall study population.[132]

Chapple et al.[65] conducted a meta-analysis of prospective, randomized, comparative trials (vs placebo or another anticholinergic) of at least 2 weeks' duration published from 1966 to 2007. The overall incidence of adverse events with most anticholinergics was significantly higher than with placebo ($p \leq 0.04$), with the exception of low-dose tolterodine IR (2 mg) and transdermal oxybutynin.[65] The authors also evaluated the risk ratio of adverse events between the various anticholinergics, and showed that some agents were associated with significantly fewer adverse events than others (table VI). For risk of any adverse event, they found tolterodine IR less likely to lead to an adverse event than oral oxybutynin IR or ER, trospium chloride IR less likely to lead to an adverse event than oral oxybutynin IR and fesoterodine less likely to lead to an adverse event than tolterodine ER.[65] None of the anticholinergics were associated with serious adverse events occurring with a significantly higher incidence than placebo – an important benchmark of safety.[65]

In most comparative trials, the overall incidence of adverse events was generally similar among the agents. In comparisons of the IR formulations of tolterodine and oxybutynin, oxybutynin was found to have a higher proportion of patients reporting ≥1 adverse event ($p < 0.05$),[68,133,134] and more adverse events per patient (2.9 vs 1.8).[135] Similarly, the incidence of adverse events appeared to be lower with trospium chloride IR 20 mg twice daily than oxybutynin IR 5 mg twice daily (65% vs 77%).[136] In this study, the 'time to event' and the incidence of possible or probable treatment-related adverse events were also significantly ($p < 0.05$) lower with trospium chloride than with oxybutynin. The risk of experiencing a possible or probable treatment-related adverse event was 0.016 in trospium chloride and 0.027 in oxybutynin recipients (relative risk [RR] for trospium chloride compared with oxybutynin 0.59); the difference was particularly apparent in the risk of experiencing dry mouth, which was 0.009 with trospium chloride and 0.021 with oxybutynin (RR 0.43).[136]

Although the incidence of systemic, moderate-to-severe, treatment-related adverse events appeared to be higher with once-daily oral tolterodine 4 mg than oxybutynin 3.9 mg TDS, transdermal oxybutynin is associated with moderate-to-severe, localized application site reactions, resulting in more patients discontinuing treatment with oxybutynin TDS despite a lower rate of dry mouth.[108]

6.1 Dry Mouth

Dry mouth is the most frequent adverse event associated with the use of oral OAB anticholinergics (table IV).[65] A Cochrane Database meta-analysis found that oral anticholinergics increased the risk of dry mouth by approximately 3-fold relative to placebo. The risk was most marked with solifenacin and least marked with trospium chloride (figure 2). Transdermal formulations of oxybutynin were not included in this analysis and darifenacin studies were excluded because the authors considered the studies to be unsuitable for meta-analysis. Fesoterodine studies had not been published at the time of the analysis.[137]

6.1.1 Data from Randomized Controlled Trials (RCTs) with Long-Acting Formulations

RCTs with long-acting formulations of anticholinergics have shown the lowest incidence of dry mouth with oxybutynin TDS (4.1–9.6%;

Table IV. Incidence of dry mouth, constipation, headache and blurred vision in 12-week, randomized, controlled trials with extended-release (ER) or once-daily (qd) formulations of anticholinergic agents[a]

Formulation	Patients in treatment group (n)	Dry mouth (%)	Constipation (%)	Headache (%)	Blurred vision (%)	Discontinuation (%)
Placebo (31 studies)[67,70-74,100-124]						
range	57–1216	1.7–9.8	1.0–9	1–6.6	0–2.6	0.8–9
median	283	5.7	3	3.7	1.7	4
Oxybutynin 10 mg qd (6 studies)[69,75,125-128]						
range	124–576	27.5–32.2	5.2–8.6	4.4–9.2	2.6[b]	3.9–9.9
median	211	28.8	6.6	6.4	2.6[b]	6.2
Oxybutynin TDS 3.9 mg/day biw (3 studies)[106-108]						
range	121–241	4.1–9.6	0.8–3.3	NR	0–1.2	10.2–11.2
median	125	7.0	2.1	NR	0.6	10.7
Oxybutynin topical gel 1 g qd (1 study)[124]	389	6.9	1.3	1.5	NR	4.9
Tolterodine ER 4 mg qd (16 studies)[67,69-75,105,108,111,113,114,125,126,129]						
range	77–599	7.3–36.9	2.0–10.2	1.0–8.3	0–2.4	1.0–6.8
median	290	22.3	5.7	5.5	1.3	4.8
Darifenacin (5 studies)[103,110,112,120,123]						
7.5 mg qd						
range	97–337	18.8–21.0	14.4–19.0	0–4.5	NR	1.0–1.5
median	229	20.2	14.8	0.9	NR	1.3
15 mg qd						
range	110–334	29.0–35.3	13.9–24.0	0–6.1	NR	2.6–9.1
median	165	31.2	19.6	4.3	NR	6.5
Solifenacin (10 studies)[100-102,104,116,119,121,122,129,130]						
5 mg qd						
range	238–578	7.7–27.6	3.7–10.6	NR	0.3–4.5	1.3–5.1
median	297	10.9	5.3	NR	3.6	2.8
10 mg qd						
range	264–1233	21.3–34.1	7.8–18.9	NR	4.0–5.6	2.6–9.3
median	406	27.4	13.2	NR	4.8	6.8
Trospium chloride 60 mg qd (2 studies)[109,118]						
range	284–298	8.7–12.9	7.5–9.4	1.0–1.8	1.0[b]	4.0–6.4
median	291	10.8	8.5	1.4	1.0[b]	5.2
Fesoterodine (4 studies)[70,105,115,117]						
4 mg qd						
range	272–554	19–21.7	3.3–5	4–4.4	NR	2.6–6
median	277	19	4	4	NR	3.95
8 mg qd						
range	279–566	33.8–36	4.5–8	2.4–3	NR	4.9–9
median	287	34.4	5.25	3	NR	6.1

a Open-label studies without comparators are not included; neither are studies of <12 weeks' duration.

b Only one study reported the incidence of blurred vision.

biw = twice weekly; **NR** = not reported; **TDS** = transdermal delivery system.

table IV).[106-108] Although direct comparative studies with the oral once-daily formulations are lacking, the reported incidence of dry mouth in 12-week RCTs was lowest with once-daily trospium chloride ER 60 mg (8.7–12.9%)[109,118] or with the lower dose of solifenacin (7.7–27.6%;

table IV).[100-102,104,116,119,121,122,129] The highest incidence of dry mouth was seen with once-daily fesoterodine 8 mg (33.8–36%).[70,105,115,117]

Incidences of dry mouth up to 61% are reported for oxybutynin 5–30 mg/day in the prescribing information; however, these data are from a pooled analysis that included dose-escalation studies of up to 4.5 months, as well as an open-label study.[23]

Dry mouth incidence is dose-dependent with solifenacin and darifenacin (table IV), occurring in 18.8–21.0% and 29.0–35.3% with once-daily darifenacin 7.5 mg[103,110,112,120] and 15 mg,[103,110,112,120,123] respectively, and in 7.7–27.6% and 21.3–34.1% with once-daily solifenacin 5 mg and 10 mg,[100-102,104,116,119,121,122,129] respectively. Similar dose-related trends in dry mouth incidence have been seen in oxybutynin ER studies utilizing doses of 5–30 mg/day.[128,138]

In RCTs with once-daily tolterodine ER 4 mg, dry mouth occurred in 7.3–36.9% of patients (table IV).[67,69,71-75,108,111,113,114,125,126,129,130] In

Table V. Incidence of dizziness/vertigo, somnolence and dyspepsia adverse events associated with anticholinergics[19-24,27,31] [a]

Agent	Adverse events (% patients)		
	dizziness/vertigo	somnolence	dyspepsia
Oxybutynin[21,22,26,31] [b]			
Oxybutynin IR 5–20 mg/day (n = 199)	16.6	14.0	6.0
Oxybutynin ER 5–30 mg qd (n = 429)	6	12	7
Oxybutynin ER 10 mg qd (n = 576)	4	2	5
Oxybutynin TDS 3.9 mg (n = 121–125)	NR	NR	NR
Oxybutynin OTG 1.0 g gel[c] (n = 389)	2.8	NR	NR
Tolterodine[23]			
Placebo (n = 683)	3	2	1
Tolterodine IR 2 mg bid (n = 986)	5	3	4
Placebo (n = 507)	1	2	1
Tolterodine ER 4 mg qd (n = 505)	2	3	3
Solifenacin[19]			
Placebo (n = 1216)	1.8	NR	1.0
Solifenacin 5 mg qd (n = 578)	1.9	NR	1.4
Solifenacin 10 mg qd (n = 1233)	1.8	NR	3.9
Darifenacin[20]			
Placebo (n = 388)	1.3	NR	2.6
Darifenacin 7.5 mg qd (n = 337)	0.9	NR	2.7
Darifenacin 15 mg qd (n = 334)	2.1	NR	8.4
Trospium chloride[18]			
Placebo (n = 590)	NR	NR	0.3
Trospium chloride IR 20 mg bid (n = 591)	NR	NR	1.2
Placebo (n = 587)	NR	NR	0.7
Trospium chloride ER 60 mg qd (n = 578)	NR	<1	1.2
Fesoterodine[25]			
Placebo (n = 780)	NR	NR	<1
Fesoterodine 4 mg qd (n = 782)	NR	NR	1.6
Fesoterodine 8 mg qd (n = 785)	NR	NR	2.3

a Data from the prescribing information are presented.

b Placebo data not reported in oxybutynin prescribing information.

c 10% weight per weight ethanol-based formulation of oxybutynin.

bid = twice daily; **ER** = extended-release; **IR** = immediate-release; **NR** = not reported; **OTG** = oxybutynin chloride topical gel; **qd** = once daily; **TDS** = transdermal delivery system.

Table VI. Adverse events that occurred with a significantly different incidence with one anticholinergic compared with another in a meta-analysis of comparative data[65]

Incidence greater or less with anticholinergic A vs anticholinergic B	Risk ratio (95% CI)	p-Value
Any adverse event		
Tolterodine IR 2 mg < oxybutynin ER 5 mg	0.59 (0.43, 0.82)	<0.01
Tolterodine IR 4 mg < oxybutynin IR 7.5–10 mg	0.83 (0.75, 0.91)	<0.01
Tolterodine IR 4 mg < oxybutynin IR 15 mg	0.86 (0.79, 0.95)	<0.01
Trospium chloride IR 40 mg < oxybutynin IR 7.5–10 mg	0.85 (0.73, 0.98)	0.02
Fesoterodine 8 mg > fesoterodine 4 mg	1.17 (1.00, 1.37)	0.04
Fesoterodine 8 mg > tolterodine ER 4 mg	1.18 (1.01, 1.37)	0.04
Adverse events leading to treatment withdrawal		
Tolterodine ER 4 mg < oxybutynin TDS 3.9 mg	0.15 (0.03, 0.66)	0.01
Tolterodine ER 4 mg < oxybutynin IR 15 mg	0.32 (0.17, 0.57)	<0.01
Tolterodine IR 4 mg < oxybutynin IR 15 mg	0.47 (0.33, 0.69)	<0.01
Oxybutynin ER 5 mg < oxybutynin ER 15 mg	0.27 (0.08, 0.92)	0.04
Dry mouth		
Tolterodine ER 4 mg < oxybutynin IR 7.5 mg	0.76 (0.57, 1.00)	0.05
Solifenacin 10 mg > solifenacin 5 mg	NR	NR
Blurred vision		
Solifenacin 10 mg > solifenacin 5 mg	NR	NR
Solifenacin 10 mg > tolterodine IR 4 mg	NR	NR
Constipation		
Solifenacin 5 mg > tolterodine IR 4 mg	NR	NR
Solifenacin 5 mg > tolterodine ER 4 mg	NR	NR
Darifenacin 15 mg > tolterodine IR 4 mg	NR	NR
Fatigue		
Tolterodine ER 4 mg > fesoterodine 4 mg	NR	NR
Tolterodine ER 4 mg > fesoterodine 8 mg	NR	NR
Nausea		
Oxybutynin IR 15 mg titrated > oxybutynin ER 15 mg titrated	NR	NR
Vomiting		
Tolterodine ER 4 mg > oxybutynin ER 7.5–10 mg	NR	NR

ER = extended-release; **IR** = immediate-release; **NR** = not reported; **TDS** = transdermal delivery system.

studies in men, the incidence of dry mouth with tolterodine was lower than the median (11–16%),[74,114] suggesting an influence of sex, although these may have been chance findings, and this has not been systematically studied. Lower rates of dry mouth (9–11%) were also seen in studies using night-time dosing.[71,114] The authors speculated that night-time dosing improved tolerability because the maximal plasma concentration of tolterodine, which occurs 4 hours after dosing, is reached while patients are usually asleep.[71] It must also be considered, however, that night-time dosing may have led to decreased absorption of the drug, and that the reduction in adverse events was due to lower serum tolterodine concentrations. In addition, this study was underpowered to show a significant difference in the primary efficacy endpoint.[71] The concept of night-time dosing leading to decreased adverse events may potentially be applicable to the other OAB anticholinergics; however, the efficacy of each drug with night-time versus daytime dosing is unknown.

6.1.2 Comparative Data

In the meta-analysis by Chapple et al.,[65] the only comparative data showing a statistically

significant difference between treatments found a lower incidence of dry mouth with tolterodine ER compared with oxybutynin IR, and with solifenacin 5 mg compared with solifenacin 10 mg (table VI).

In clinical trials, ER formulations of oxybutynin and tolterodine were associated with a lower incidence of dry mouth compared with their respective IR formulations.[139,140] Dry mouth incidence was lower with tolterodine ER than oxybutynin ER in the OPERA trial.[75]

Some other agents have been compared with oxybutynin IR, and show a lower incidence of dry mouth. Dry mouth incidence was lower with trospium chloride IR 20 mg twice daily than oxybutynin IR 5 mg twice daily (33% vs 50%; $p < 0.01$); the high dry mouth rates reported may have been related to use of a questionnaire to assess incidence rather than the more commonly used spontaneous reporting of adverse events.[136] Dry mouth incidence was also lower with once-daily darifenacin 15 mg (maximum recommended dose) than oxybutynin 5 mg three times daily (13% vs 36%; $p < 0.05$).[66]

6.2 Constipation

Constipation is another adverse event commonly reported with OAB anticholinergics.[19-25] Several factors complicate the analysis of reports of constipation in patients receiving antimuscarinic agents. There is no standard definition for constipation, and the rates reported in clinical trials typically depend on subject self-reporting. Constipation is a common complaint, particularly among the elderly;[141] therefore, many patients may have baseline constipation prior to beginning drug therapy. Agents that contribute to or worsen constipation may lead to serious complications for some patients.[142,143]

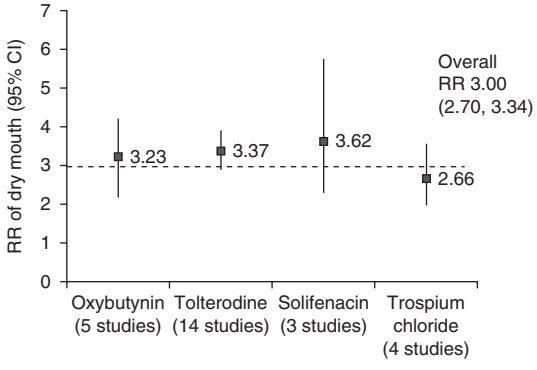

Fig. 2. The relative risk (RR) of dry mouth from a meta-analysis of placebo-controlled trials with oral anticholinergic agents oxybutynin, tolterodine, solifenacin and trospium chloride. Transdermal formulations of oxybutynin were not included in this analysis.[137]

6.2.1 Data from RCTs with Long-Acting Formulations

Among the once-daily formulations of anticholinergics, the lowest incidence of constipation was reported with oxybutynin TDS (0.8–3.3%)[106-108] and oxybutynin gel (1.3%),[124] and the highest with darifenacin (13.9–24.0%; table IV).[103,110,112,120,123] This may be due to to the M_3 selectivity of darifenacin. In a comparative study, the incidence of constipation was similar during treatment with once-daily darifenacin 15 mg (10%) and three-times-daily oxybutynin 5 mg (8%).[66]

Constipation rates are dose-dependent with darifenacin and solifenacin. Elderly patients may be at greater risk of constipation with these agents. The highest incidence of constipation was seen in elderly patients at the highest dosages: 24% with once-daily darifenacin 15 mg[110] and 17.2% with once-daily solifenacin 10 mg.[121] Constipation rates as high as 50% were reported in elderly patients in an RCT with oxybutynin IR,[144] but in this study the incidence of constipation in the placebo group was similarly high (45%), underscoring that this is a common complaint in elderly patients regardless of treatment.

6.2.2 Comparative Data

In the meta-analysis by Chapple et al.,[65] comparative studies showed a similar incidence of constipation for most comparisons between anticholinergics, but significantly higher rates with solifenacin 5 mg compared with tolterodine IR or ER 4 mg, and with darifenacin 15 mg compared with tolterodine IR 4 mg (table VI).

6.3 Headache

The incidence of headache with anticholinergics is generally low and is therefore not always reported in clinical trials (particularly those that report events occurring in ≥3–5% of patients).

In fact, in randomized trials of the once-daily formulations, the incidence of headache with active treatment ranged from 0% to 9.2% and was similar to that observed with placebo (1.0–6.6%; table IV).

6.3.1 Data from RCTs with Long-Acting Formulations

The incidence of headache reported in RCTs with long-acting formulations ranged from 0% in elderly patients receiving once-daily darifenacin 7.5 or 15 mg[110] to 9.2% in women receiving once-daily oxybutynin 10 mg (table IV).[127] Headache rates were consistently low (<2%) in both studies with once-daily trospium chloride ER 60 mg.[109,118] Headache incidence was not reported in any of the solifenacin studies analysed.[100-102,104,116,119,121,122,129] With tolterodine ER, the headache incidence in 12-week RCTs ranged from 1.0% to 10.2% (table IV). The lowest rate was reported in men[74] and the highest in treatment-naïve women.[69]

6.3.2 Comparative Data

The incidence of headache was generally similar in comparative trials with oxybutynin and tolterodine, even when comparing IR and ER formulations.[68,75,113,133,135,145] The incidence of headache was lower with trospium chloride IR 20 mg twice daily than oxybutynin IR 5 mg twice daily (4% vs 9%) in a comparative study.[136]

These findings are generally consistent with a meta-analysis of comparative studies that showed no significant difference in the incidence of headache between various anticholinergics.[139]

6.4 Blurred/Abnormal Vision

6.4.1 Data from RCTs with Long-Acting Formulations

In trials with long-acting agents, the highest incidence of blurred vision (4.0–5.6%) was seen with solifenacin 10 mg/day (table IV).[100-102,104,116,119,122] Solifenacin 5 mg/day was associated with rates of 0.3–4.5%.[100-102,104,116,119,122,129] Blurred vision incidence was not reported in any of the darifenacin[103,110,112,120,123] or fesoterodine studies analysed.[70,105,115,117] With the other long-acting agents, the incidence of blurred vision was consistently <3% (table IV), i.e. trospium chloride ER 1.0%,[118] oxybutynin ER 2.6%[127] and tolterodine ER 0–2.4%.[67,71-73,129,130] The 0% incidence was reported in a study in which patients took tolterodine ER at night, again suggesting that night-time dosing may decrease the potential for adverse events.[71]

6.4.2 Comparative Data

In a meta-analysis of comparative studies, the incidence of blurred vision was not significantly different between most agents, with the exception of a lower incidence with tolterodine IR compared with solifenacin.[139]

6.5 Dyspepsia

6.5.1 Comparative Data

In the meta-analysis by Chapple et al.,[65] no significant differences in dyspepsia risk were seen among the anticholinergics, although nausea was significantly more common with oxybutynin IR than oxybutynin ER. In comparative trials, dyspepsia incidence was significantly lower with tolterodine IR than oxybutynin IR in a pooled analysis of four randomized trials,[135] but was similar with tolterodine IR (5.2%) and oxybutynin ER (5.9%) in the OBJECT (Overactive Bladder: Judging Effective Control and Treatment) study.[145] These results were generally supported by results from other studies.[67,146] Dyspepsia incidence was 5% with trospium chloride IR and 3% with oxybutynin IR in a randomized comparative study.[136] Dyspepsia does not appear to occur to any measurable degree with oxybutynin TDS.[27,106-108]

7. Adverse Effects and Treatment Adherence

Since OAB is a chronic condition, long-term adherence to therapy is important.[147] Factors that may contribute toward treatment adherence include occurrence of treatment-related adverse effects, complexity of drug regimens, and efficacy.[147] In a survey of patients with incontinence, lack of efficacy, adverse effects and cost were the three most commonly cited reasons for discontinuing treatment.[148] Thus, anticholinergics that have fewer adverse effects and less complicated

regimens (e.g. once-daily administration) may contribute toward better adherence.

During RCTs of 12 weeks' duration, discontinuation rates were low (<10% for all agents except oxybutynin TDS) [table IV]. Although oxybutynin TDS is associated with the lowest incidence of systemic anticholinergic adverse events, application site reactions cause a number of patients on this therapy to stop treatment.[106-108]

Anticholinergics are generally well tolerated during long-term therapy, with most adverse events being mild in severity.[136,146,149-154] Treatment-emergent serious adverse events were reported in 7–12% of patients receiving tolterodine (IR or ER), oxybutynin or darifenacin therapy, with 0.3–0.7% considered to be treatment related.[146,149,150,152] Adverse events reported during long-term (≤2 years) therapy were generally similar to those occurring during short-term (<12 weeks) therapy.[136,146,149-154]

In clinical trials, the proportion of patients persisting with therapy after long-term treatment with tolterodine (IR or ER), oxybutynin, solifenacin, darifenacin or trospium chloride was generally high, and discontinuation rates were ≤30% (table VII).[136,146,149-154] Adverse event-related discontinuation rates in these trials were 4–15%,[136,146,149-154] with dry mouth accounting for 0.4–5% of withdrawals.[146,149-152] However, it should be kept in mind that persistence rates in real-life clinical settings may be different from those seen in clinical trials.[33] Indeed, a large database study showed that only 55.5% of patients refilled their index prescription and only 13.2% persisted on their index medication for 1 year.[10] Similar results were observed in other database studies.[155,156]

As noted earlier in this section, persistence with therapy may be influenced by attributes of the drug. Database analyses have shown better adherence and persistence with therapy in patients receiving tolterodine compared with oxybutynin.[157,158] Similarly, in a Danish database analysis, long-term persistence was higher with trospium chloride than with all other OAB antimuscarinics assessed.[159] Moreover, persistence rates were better with drugs administered once daily than those administered twice or three times daily, as shown in database analyses with oxybutynin and tolterodine.[10,155,157]

8. Impact of Trial Design on Adverse Event Rates

It is apparent from clinical studies with flexible- and fixed-dose design that the type of study design can affect the incidence of adverse events reported in a study. In a randomized, fixed-dose study, 'responders' and 'non-responders' are randomized to lower and higher dose groups, while in a voluntary flexible dose-titration study (which is more akin to how the drug would be used in the clinical setting), individual patients are up-titrated to the dose with an optimal efficacy/adverse effect ratio. In a flexible-dose study, the patients may choose to stay on the lower dose ('responders') and not titrate to the higher dose ('non-responders'); therefore, the lower dose is likely to be associated with a higher incidence of adverse events than the same dose in a randomized fixed-dose study.

Table VII. Treatment discontinuation rates in long-term clinical trials following long-term therapy with commonly available anticholinergics[136,146,149-153]

Agent	Duration of follow-up (mo)	Discontinuation rate (% patients)	
		overall	due to adverse events
Oxybutynin IR[136]	12	26.7	10
Tolterodine IR[146,149]	9–12	30–38	9–15
Tolterodine ER[150,152]	12	23–29.4	9.9–10.1
Solifenacin succinate[121,151]	9–12	18.6–20.0	4.7–9.2
Darifenacin[153,154]	24	33.7–36.0	8.9–15.9
Trospium chloride IR[136]	12	25.0	6.0

ER = extended-release; **IR** = immediate-release.

Patients receiving the higher doses are likely to be 'non-responders' with lower adverse event rates, while patients remaining at the lower doses will be 'responders' with higher adverse event rates. This means that, with flexible dosing, the proportion of patients with adverse events will be higher in the lower dose group and lower in the higher dose group, compared with what is expected based on data from randomized, phase III studies cited in the prescribing information.

Clear discrepancies between adverse event rates with fixed- and flexible-dose studies can be seen from studies of solifenacin, darifenacin and fesoterodine, which have been studied in both fixed-dose, randomized, phase III studies and in flexible-dose studies.

With solifenacin, while most studies reported an incidence of dry mouth of around 8–17% with solifenacin 5 mg once daily, the flexible-dose titration STAR (Solifenacin Tolteradine A R) study reported an incidence of 27.6%[129] with this dose, compared with a rate of 10.9% reported in the prescribing information.[20] For constipation, although higher rates were reported with solifenacin versus tolterodine in randomized studies, the dose-titration STAR trial reported a generally similar incidence and severity of constipation in patients receiving solifenacin or tolterodine ER.[130] Constipation of mild severity occurred in 3.2% of solifenacin and 1.3% of tolterodine ER recipients in the STAR trial; corresponding rates for moderate constipation were 2.7% and 1.0%.[130]

Discrepancies can also be seen when comparing adverse event rates for darifenacin in dose-titration and fixed-dose studies. The incidence of dry mouth reported in the prescribing information from three 12-week, fixed-dose, placebo-controlled, phase III studies with darifenacin were 20.2% and 36.3% for the 7.5 mg and 15 mg doses, respectively,[21] whereas in the dose-titration study the incidence of dry mouth was 20.4% for those who remained on the 7.5 mg dose and 17.5% for those who had increased to the 15 mg dose at 12 weeks.[120] Differences in rates of constipation with darifenacin can also be seen when comparing data from dose-titration studies with data from fixed-dose studies. In the three 12-week, fixed-dose, placebo-controlled, phase III trials of darifenacin, constipation was reported in 14.8% and 21.3% of patients receiving darifenacin 7.5 and 15 mg, respectively.[21] In the dose-titration study, the overall incidence of constipation was 20.9%; however, the rate was slightly lower among patients who were titrated to the 15 mg dose (20.0%) compared with those who remained at the 7.5 mg dose (22.2%).[120]

Similarly, for fesoterodine, in a 12-week, flexible-dose study of fesoterodine 4 or 8 mg in 883 patients with OAB, constipation was reported in 11% of patients in the flexible-dose study,[160] higher than the 4% or 6% with fesoterodine 4 and 8 mg, respectively, stated in the prescribing information, taken from randomized, controlled, fixed-dose trials.[26] In the flexible-dose study, 63% of patients chose to increase their dose from 4 to 8 mg after 2 weeks; adverse event rates for specific dose groups were not reported.[160] The incidence of dry mouth observed in the flexible-dose study with 4 or 8 mg doses (26%)[160] was similar to that reported in the prescribing information (19% and 35% with fesoterodine 4 and 8 mg, respectively).[26]

9. Conclusions

Although all OAB anticholinergics are effective in reducing symptoms of OAB, they differ in their molecular structure (quaternary or tertiary amine), physicochemistry, route of metabolism (including the formation of active metabolites and potential for DDIs), route of excretion, potential for local activity in the bladder after renal excretion, receptor binding profiles, method of delivery (transdermal or oral) and formulation (ER or IR), all of which may influence their efficacy and incidence of associated adverse effects. The tolerability profiles of the currently available agents are markedly different from one another.

Since OAB is a chronic disease requiring long-term therapy, often in elderly patients, careful assessment of the pharmacological, safety and tolerability profiles of the anticholinergic agent is needed before prescription, in order to tailor therapy to the individual patient's clinical needs, and thereby maximize the chance of treatment success and long-term adherence to therapy.

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