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REVIEW ARTICLE

Antimuscarinics for the treatment of overactive bladder: understanding the role of muscarinic subtype selectivity

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Abstract
Introduction and hypothesis Antimuscarinic agents appear to exert their therapeutic activity in overactive bladder (OAB) via blockade of the M_3 muscarinic receptor subtype. Antimuscarinics are broadly similar in efficacy, but their safety and tolerability profiles vary, which may reflect differences in muscarinic receptor selectivity profiles.
Methods This review of available literature aims to determine whether antimuscarinic agents with greater M_3 selectivity have clinical advantages over less selective drugs.
Results Antimuscarinic agents differ widely in their propensity to cause cognitive and cardiovascular (CV) effects, which appear mainly to be related to differences in their relative selectivity for binding to non-M_3 receptors, including M_1 receptors in the brain and cardiac M_2 receptors.
Conclusions Cognitive and CV effects are especially pertinent for the OAB patient who tends to be older with various comorbidities and is often taking multiple medications. Hence, it is important to consider the risk/benefit balance of antimuscarinic agents when selecting OAB treatment.

Keywords Antimuscarinics · Cardiovascular · Cognitive function · Muscarinic · Overactive bladder · Receptor selectivity

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Introduction

It is well documented that there are five muscarinic receptor subtypes (M_1–M_5) which are widely distributed throughout the body [1, 2]. Each receptor subtype mediates distinct functions according to its location within the body. Although the same receptor subtype can be located in different areas of the body, some subtypes predominate in particular organs and/or tissues. The main locations and roles of the receptor subtypes are shown in Table 1 [1–8]. However, the precise functions and distribution of each of the muscarinic receptors remains to be fully clarified.

The bladder detrusor muscle contains all five muscarinic subtypes, but it is the M_3 subtype that principally mediates bladder contractions [9]. Overactive bladder (OAB) is the terminology used to describe a clinical syndrome characterized by various urinary symptoms, i.e., urinary urgency, with or without urge incontinence, usually with increased frequency of micturition and nocturia, and in the absence of urinary tract infection or other obvious pathology [10]. As normal and abnormal contractions of the human bladder occur predominantly via the M_3 receptors in the bladder detrusor muscle [11], this receptor subtype may be considered an important target in the pharmacotherapy of OAB.

Muscarinic receptor antagonists, such as the antimuscarinics, are the mainstay of OAB pharmacotherapy. The mechanisms of action of these agents are currently believed to be via blockade of the muscarinic M_3 receptors located on the detrusor smooth muscle of the bladder causing a mechanical, myogenic effect [3].

The currently available antimuscarinic agents have different receptor binding profiles. This review highlights the impact of receptor antagonism with respect to darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and

Table 1 Predominant locations and role of muscarinic receptor subtypes [1–8]

Subtype	Distribution	Role
M_1	Brain (cortex, hippocampus); salivary glands	Cognitive functioning and memory; saliva secretion
M_2	Heart; brain; smooth muscle	Regulation of heart rate and heart rate variability; behavioral flexibility
M_3	Smooth muscle; glands; eye	Smooth muscle contraction; gland secretion; iris contraction
M_4	Brain (forebrain, striatum)	Modulation of several important dopamine-dependent behaviors
M_5	Brain (substantia nigra); eye	Regulation of striatal dopamine release

trospium and aims to determine whether the medications with greater M_3 selectivity have clinical advantages over the less selective drugs. In particular, the potential relationship between different receptor subtype selectivity and adverse effects associated with available antimuscarinic treatments is examined.

Antimuscarinics and M_3 receptor selectivity

Although the antimuscarinics have similar efficacy in reducing the symptoms of OAB [12, 13], they vary in their safety and tolerability profiles, possibly as a result of differing selectivity for muscarinic receptor subtypes. Several studies have evaluated the relative in vitro binding affinities of antimuscarinic agents to the different receptor subtypes (Table 2) [14–18]. Data have shown darifenacin to have the highest selectivity for M_3 receptors over other receptor subtypes (M_1, M_2, and M_4) compared with other commonly used antimuscarinics, including oxybutynin, propiverine, solifenacin, and tolterodine [16].

Understanding the impact of receptor selectivity is important to enable physicians to make informed decisions regarding the use of antimuscarinics for the treatment of OAB. The prevalence of OAB increases with age [19–21], and this may influence treatment choice. Comorbid conditions [e.g., age-related cognitive decline, cardiovascular (CV) problems] can become more common with age (Fig. 1), and the potential for polypharmacy and pharmacotherapy-related adverse events (AEs) increases [22–26].

Antimuscarinics and the impact of receptor subtype antagonism on tolerability and safety

The class AEs such as dry mouth, constipation, and blurred vision are well known and widely reported [12, 13, 27, 28], and consistent with the ability of the antimuscarinic agents to block M_3 receptors in the salivary glands, gastrointestinal smooth muscle, and ciliary and iris sphincter muscles, respectively [29]. However, discontinuations due to AEs with active treatment are generally infrequent in controlled trials, with a similar rate to that of placebo [29]. As they are widely recognized, they will not form the focus of this review.

It has become increasingly apparent that these agents are also associated with differential effects on cognitive and cardiac parameters [30–32]. These adverse effects are believed to be a consequence of the antimuscarinic drugs binding to receptor subtypes that have minimal or no involvement in bladder detrusor contractions, i.e., the M_1,

Table 2 Relative mean M_3 affinity of commonly used antimuscarinics

Ratio of affinity	Muscarinic receptor subtype			
	M_3 vs. M_1	M_3 vs. M_2	M_3 vs. M_4	M_3 vs. M_5
Darifenacin[a]	16	53	26	4.1
Fesoterodine[b]	0.2	0.5	1.3	0.8
Oxybutynin[a]	1.8	6.2	1.9	5.3
Solifenacin[a]	2.2	15	9.1	2.6
Tolterodine[a]	0.6	0.95	1.5	0.6
Trospium[c]	1.5	1.3	2.0	4.6

[a] Relative mean affinities calculated as the ratio of K_i values as reported by [16]

[b] Relative mean affinities calculated as the ratio of K_i values determined from the antilog of pK_i values as reported by [17]

[c] Relative mean affinities calculated as the ratio of K_i values as reported by [18]

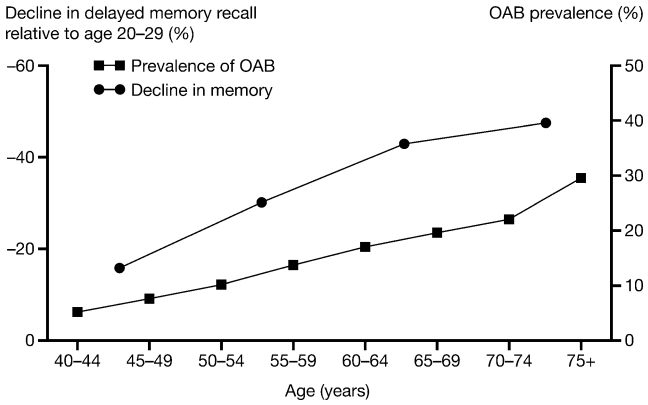

Fig. 1 Prevalence of overactive bladder (*OAB*) and memory loss (compared against a young age group) increases with age [22, 26]

M_2, M_4, and M_5 muscarinic receptors (Table 1). Tolerability may be a key reason for low adherence and persistence seen with OAB medications [33, 34]. The differential receptor subtype selectivity of the different agents (Table 2) has the potential to lead to adverse effects of differing extent, and this will be explored further in the sections below.

Cognitive function

The potential for impairment of cognitive function is an important factor in the decision to prescribe antimuscarinics and is especially pertinent in a condition that increases in prevalence with age (Fig. 1) [35]. Cognitive function can be affected by various intrinsic factors (e.g., age or genetic conditions), comorbid pathologies (e.g., neurodegenerative, vascular, or metabolic disorders), or external factors (e.g., sociocultural influences, drug treatment, or trauma) [36].

Cognitive function, comorbidities, and polypharmacy

Patients with OAB are likely to suffer from various comorbidities that may affect blood–brain barrier (BBB) integrity or cognitive function, such as multiple sclerosis, dementia, and atherosclerosis [37]. As in patients with idiopathic OAB, antimuscarinics remain the principal treatment for neurogenic OAB, e.g., in patients with multiple sclerosis [38, 39]. Therefore, it is important to avoid the use of drugs that impair cognitive function in patients with comorbidities that themselves contribute to cognitive dysfunction, and particularly in patients with progressive neurological disorders whose cognitive function continues to decline throughout the disease course. Although there has been considerable interest in the effects of antimuscarinics in patients with OAB, there are limited studies evaluating the effect of antimuscarinics on cognition in patients with neurogenic OAB, and this warrants further investigation.

It is likely that many patients with OAB will be using multiple co-medications, including those with cholinergic activity, which can cause cumulative detrimental effects on cognitive function [40, 41]. A study in community-dwelling older persons showed that the prevalence of cognitive impairment more than doubled with the use of drugs with anticholinergic activity [42]. OAB management strategies should ensure that medications are evaluated to avoid prescribing agents with potential drug–drug interactions, including mechanisms of actions and side effect profiles. For example, it may be prudent to avoid the administration of anticholinergics for OAB therapy at the same time as cholinesterase inhibitors, which are typically used to improve memory and cognition in Alzheimer's disease [43]. Hence, when selecting a specific antimuscarinic agent for an individual OAB patient, it is important to consider the propensity for CNS-related side effects in the context of that particular patient's clinical profile.

Accumulating evidence indicates that the potential for the different antimuscarinic drugs to adversely affect cognitive function varies from agent to agent. The receptor selectivity profiles of the antimuscarinics play an important role in these CNS effects, but it should be noted that these adverse effects are also related to differing pharmacokinetic properties (e.g., ability of the molecule to enter the CNS) of these agents. The other key factors that contribute to cognitive impairment with antimuscarinic therapy include the integrity of the BBB in limiting the entry of these agents into the CNS, the ability of a drug to accumulate within the brain, and the extent of interaction the drug has with M_1 receptors located in the brain.

Antimuscarinic agents and CNS penetration

Entry into the brain via the BBB by passive diffusion is dependent on molecular size, polarity, and lipophilicity. In addition, active transport via p-glycoproteins and the multidrug resistance proteins may reduce penetration and accumulation of agents in the brain (Table 3) [16–18, 25, 30, 44–48]. Highly lipophilic, non-polar small molecules will more readily cross the BBB by passive diffusion (e.g., oxybutynin, 357 kDa), whereas larger molecules, such as darifenacin, solifenacin, tolterodine, and fesoterodine (all >475 kDa), are unlikely to cross the BBB by passive diffusion. As a hydrophilic, polar compound (428 kDa) trospium also has a low propensity for BBB penetration. These properties are applicable under normal physiological circumstances, but a variety of conditions may reduce the integrity of the BBB.

Limited research has been conducted examining the accumulation of antimuscarinic agents within the brain. Preclinical studies have indicated that CNS penetration and accumulation is minimal with darifenacin and tolterodine

Table 3 Cognitive potential of antimuscarinic drugs used in the treatment of overactive bladder

	Darifenacin	Fesoterodine	Oxybutynin	Solifenacin	Tolterodine	Trospium
M_3:M_1 relative selectivity	16	0.2	1.8	2.2	0.6	1.5
Size (MW, kDa)	Large (507.5)	Large (527.7)	Small (357.5)	Large (480.6)	Large (475.6)	Intermediate (427.9)
Polarity (pK_a)[a]	Positive (9.20)	Positive	Neutral (6.96)	Positive (8.5)	Positive (9.87)	Highly polar
Relative lipophilicity (LogP)[b]	Low (2.7)	Very low (0.47)	High (3.3)	Low (1.69)	Low (1.83)	Extremely low (−1.22)
Active efflux mechanism	PGP	N	No	No	No	PGP
CNS/plasma concentration ratio[c]	10–29%	4–7%	40–60%	N	18–67%	17%
Brain receptor occupancy[d]	Undetectable levels	N	1.4–3.4	8.1–46.7	3.6–17.9	N

PGP p-glycoprotein, *N* no data reported, *CNS* central nervous system

[a] Low polarity with low pK_a (i.e., weakly acidic/basic drugs) are associated with greatest ability to partition into lipid membranes

[b] Lipophilicity and high solubility in ethanol reflect ability to partition into the lipid membranes of the blood–brain barrier; passive diffusion across lipid membranes is greatest for drugs with values of 1–3 for Log*P* (the logarithm of the ocanol/water partition coefficient)

[c] Concentration achieved post-dose in animal studies in various brain regions relative to plasma concentrations at the same time points

[d] Selectivity for bladder over the brain across increasing doses

[49–51], whereas oxybutynin appears to accumulate within the brain at somewhat higher concentrations [52, 53]. A preclinical study on muscarinic receptor selectivity for bladder over brain demonstrated that this ratio was relatively large for solifenacin (8.1–46.7 across doses tested) and tolterodine (3.6–17.9) compared with oxybutynin (1.4–3.4) [51]. The ability of an antimuscarinic drug to persist within the brain may also be influenced by the presence of efflux mechanisms. Specific active transport mechanisms mediated by p-glycoproteins have been identified for darifenacin and trospium [44, 54].

When an antimuscarinic agent is able to cross the BBB into the brain and be retained in sufficient concentrations to exert any effects, the degree to which it interacts with muscarinic receptors depends on the individual agent's receptor selectivity profile. Although all five receptor subtypes are expressed in the brain [3], M_1 and M_2 receptors are important in cognitive functioning and memory, and behavioral flexibility and learning, respectively [7, 55–57]. As there is now considerable evidence demonstrating that blockade of central M_1 receptors has a key functional role in cognitive impairment, e.g., memory loss, it follows that antimuscarinic agents with affinity for this receptor subtype may be associated with CNS side effects [3]. Therefore, antimuscarinic agents may be expected to have differing effects on cognition depending upon their binding selectivity for muscarinic subtype receptors.

Antimuscarinic agents and cognitive impact

Data from clinical studies (mainly with healthy participants) have supported the hypothesis that agents with affinity for M_1 receptors may be associated with CNS effects. Studies have shown that non-selective antimuscarinics, such as oxybutynin, have been associated with more cognitive adverse effects than the selective antimuscarinics, such as darifenacin, tolterodine, and solifenacin [30, 55] (Table 4). Currently, darifenacin has the most compelling evidence demonstrating no impairment of memory or other cognitive functions in three placebo-controlled, randomized controlled trials [30, 58–60]. In a parallel-group, 3-week study designed to investigate the effects of antimuscarinics on cognitive function, 150 healthy participants (≥60 years of age) were randomized to receive one of three treatments: oxybutynin ER (10, 15, and 20 mg once daily in weeks 1, 2, and 3, respectively); darifenacin (7.5 mg once daily in weeks 1 and 2 and 15 mg once daily in week 3); or placebo [58]. Cognitive function was assessed through a battery of computerized cognitive function tests, including immediate and delayed memory recall (name–face association and recognition tests) and visual attention tests [58]. It was concluded that darifenacin had no significant effects on memory vs. placebo.

Table 4 Antimuscarinics with clinical studies evaluating effects on cognitive function

Antimuscarinic	Patient population	Cognitive effect	Key clinical outcomes
Darifenacin vs. oxybutynin [58]	Healthy volunteers (n=150), aged≥60 years	Darifenacin− Oxybutynin+++	Delayed recall not significantly different between darifenacin and placebo. Significant impairment in delayed recall with oxybutynin
Darifenacin [59]	Healthy men (n=27), aged 19–44 years	Darifenacin−	No significant effect on computerized cognitive function tests
Darifenacin [60]	Volunteers (n=129) with no/mild cognitive impairment, aged ≥60 years	Darifenacin−	Darifenacin was not significantly different from placebo
Tolterodine vs. oxybutynin [61]	Healthy volunteers (n=17), mean age 63.4 years	Tolterodine− Oxybutynin+++	No significant change in delayed recall over treatment with tolterodine. Delayed recall significantly impaired with oxybutynin
Solifenacin [62]	Healthy older volunteers (n=12)	Solifenacin−	No statistically significant cognitive deterioration with solifenacin vs. placebo
Trospium [63]	Older adults with OAB (n=12), aged 65–75 years	Trospium−	No significant net drug effect on learning or memory recall

− No/limited cognitive impact, +++ Significant impact

Performance on a battery of cognitive tests was also similar for darifenacin and placebo in a study of 129 elderly healthy volunteers (aged ≥65 years) with no/mild cognitive impairment [60].

Several small clinical studies have provided preliminary evidence that tolterodine has no significant effects on cognitive function in adults and children with either idiopathic or neurogenic OAB [61, 62, 64]. A small, double-blind 3-week study of tolterodine ER 4 mg was conducted in healthy older subjects (n=22) not receiving any concomitant anticholinergic or CNS active medications [61]. It was concluded that tolterodine did not affect recent memory performance in older subjects. Similarly, a small crossover study of patients with neurogenic OAB (n=14) receiving tolterodine or oxybutynin showed that tolterodine was associated with better performance on cognitive function tests [65]. In a randomized, double-blind, placebo-controlled crossover study in healthy volunteers, there were no impairments of cognitive function following single doses of tolterodine [66]. In addition, tolterodine was not associated with any decline in memory or attention span in children (n=14, aged 5–11 years) with urgency or urgency incontinence after 2 weeks' treatment [64]. However, case studies have reported that tolterodine treatment may be associated with memory loss, mental confusion, and aggregating hallucinations in patients with OAB. These effects have been noted in both younger (46 years of age) and older (≥66 years of age) adult patients and warrant further investigation [67–69].

There are limited data investigating cognitive function in patients treated with solifenacin or trospium, but findings so far indicate that neither agent appears to lead to cognitive deterioration [62, 63, 66, 70]. A pilot study in 12 healthy elderly participants demonstrated that a single dose of solifenacin 10 mg did not appear to impair cognitive function [62], while three studies (n=12 or 24 per study) showed that trospium (45 or 60 mg once daily) had no effect on cognitive function, learning, or recall in older patients with OAB (aged 65–75 years) and normal cognitive function in healthy volunteers [63, 66, 70].

In contrast to the evidence accumulated for darifenacin, tolterodine, solifenacin, and trospium, the data for oxybutynin are somewhat mixed. Although there is some evidence to suggest that oxybutynin does not affect cognitive function [three studies: two in healthy participants (n=24 per study) and one in children with OAB symptoms (n=14)] [64, 66, 70], the majority of clinical studies conducted [four studies: three in healthy volunteers (n=12–150) and one in patients with neurogenic OAB (n=14)] have found that oxybutynin treatment is associated with significant memory deterioration and impairment of several other measures of cognitive function [58, 61, 62, 65]. Furthermore, published case studies have also suggested that oxybutynin may induce memory loss and psychosis. In a recent case report, a 66-year-old female with OAB presented with memory loss secondary to oxybutynin use, which resulted in non-adherence to all medication [71]. This patient's memory and subsequent adherence to medication improved within 3 weeks following discontinuation of oxybutynin. A report of two cases (a 7-year-old boy and a 21-year-old man) has also provided evidence that oxybutynin may produce psychotic disorders [72].

Association between receptor selectivity and effect on cognition

Many of the aforementioned cognitive function studies were small, and the findings should be interpreted with

caution. However, the observed differential effects of antimuscarinics on cognition may reflect differences in their binding properties. Darifenacin has demonstrated a selectivity of 16:1 for the M_3 receptor over the M_1 subtype in a competitive binding study (Table 2) [16]. Furthermore, in a recent study on the binding properties of commonly used antimuscarinics, darifenacin was shown to occupy few brain muscarinic receptors compared with bladder receptors (Table 3) [53]. Solifenacin had a selectivity of 2:1 for the M_3 receptor over the M_1 subtype (Table 2) and, despite its large molecular weight, showed a significant occupancy of brain muscarinic receptors (Table 3) [53]. However, solifenacin shows higher selectivity for bladder smooth muscle cells (Table 3), which are known to express more M_3 receptors compared with other tissues [73]. Tolterodine is a non-selective muscarinic antagonist (Table 2), but like solifenacin, it appears to have high selectivity for the bladder over the brain (Table 3) [53]. In contrast, oxybutynin is not only relatively non-selective for M_3 receptors over M_1 (affinity of >2:1, Table 2) but also shows a significant occupancy of brain muscarinic receptors, which may reflect the high lipophilicity and smaller molecular weight of this drug compared with tolterodine and solifenacin (Table 3) [53, 74]. In a study using positron emission tomography in rhesus monkeys, oxybutynin occupancy of muscarinic receptors within the brain was significant (40–60%) [51]. Oxybutynin was also shown to have low selectivity for the bladder over brain receptors (Table 3) [53]. As a highly polar, hydrophilic compound that is actively transported by a p-glycoprotein (Table 3), trospium has a low propensity to cross the BBB [30, 44]. Hence, although it is a relatively non-selective antimuscarinic agent [15], it may have a low potential to affect cognition provided that the BBB integrity is not compromised, as suggested in the studies cited above.

As the CNS effects of non-selective muscarinic blockade within the brain are not completely predictable [55], it is important to consider other aspects of the drug, or the full patient clinical history/condition when selecting a treatment. Antimuscarinic-induced cognitive impairment will be particularly troublesome in vulnerable populations who may already experience compromised CNS function, such as the elderly and those with neurogenic OAB caused by conditions such as multiple sclerosis and Parkinson's disease.

Cardiovascular effects

The older population tend to have a higher prevalence of OAB [26], CV comorbidities [75, 76], and an increased underlying risk for CV events. The high prevalence of CV disease in patients with OAB was reported in a database study of 13,214 adult patients with OAB [24]. This study found that patients with OAB were significantly more likely to have CV comorbidities compared with age- and gender-matched non-OAB patients (39% vs. 21%, respectively, $p<0.0001$; Fig. 2), with hypertension being the most common preexisting condition [24]. As elevated heart rate (HR) predicts increased CV risk, a second database analysis assessed the baseline HR of OAB patients on the day that the first OAB drug prescription was obtained [24]. Results showed that in patients with OAB ($n=16{,}258$) who initiated antimuscarinic treatment, a large proportion (39%) had an elevated HR of ≥80 bpm.

All antimuscarinics have the potential to increase CV risk via a non-selective blockade of cardiac M_2 receptors

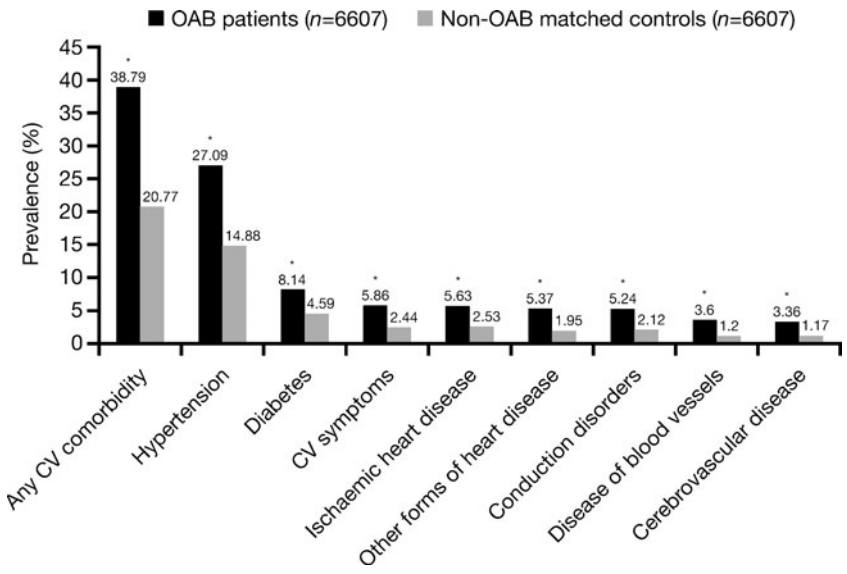

Fig. 2 Prevalence of cardiovascular (*CV*) comorbidity at the time of overactive bladder (*OAB*) diagnosis in a US cohort and matched control group [24]. *$p<0.001$ vs. non-OAB-matched controls

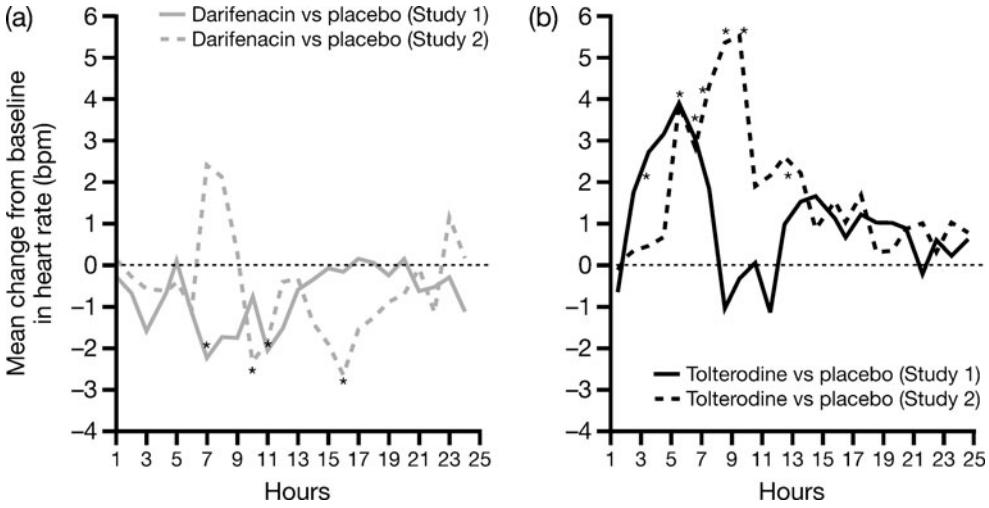

Fig. 3 Changes in hourly heart rate over 24 h following darifenacin (**a**) and tolterodine (**b**) in two studies of healthy volunteers [31, 32]. *$p<0.05$. *bpm* beats per minute

[76]. Although other muscarinic receptor subtypes are located in the heart (M_1, M_3, and M_5), their functions are yet to be fully elucidated. M_2 receptors in the heart modify pacemaker activity and atrioventricular function, altering the contractile force in the atrium and ventricles; only this muscarinic receptor subtype appears to be involved in regulating HR. Consequently, the blockade of M_2 receptors reduces the down-regulation of HR by lowering the effect of acetylcholine on the receptors. This leads to increased HR and possibly tachycardia, causing an increase in oxygen demand by the myocardium [76]. Although the clinical effects of increased HR have not been demonstrated specifically in OAB patients, epidemiological studies have linked increased resting HR with increased mortality and morbidity in different populations, including initially healthy individuals [77–79].

HR variability (HRV) has been used as a surrogate measure of autonomic influences on the heart and is indicative of adverse changes in the parasympathetic/sympathetic balance [80]. A decrease in HRV has been associated with an increased risk for cardiac events, such as myocardial infarction [81], and increased CV risk factors, such as high blood pressure and coronary artery calcification [82]. In a large community-based population from the Framingham Heart Study, a small decrease in HRV (one standard deviation) over 2 h was associated with a 41% increased risk of cardiac events [81].

The different antimuscarinic agents exert differential effects on cardiac parameters, such as HR and HRV [31, 32]. As with cognitive function, this may be due to the different binding profiles of the antimuscarinics [16]. Agents highly selective for M_3 receptors over M_2 receptors are likely to have less effect on HR compared with non-selective antimuscarinics [1, 76]. Darifenacin has demonstrated a selectivity of 53:1 for the M_3 receptor over the M_2 subtype in a competitive binding study (Table 2) [16]. Solifenacin and oxybutynin also demonstrated selectivity for M_3 over M_2 receptors, but to a lesser extent (15:1 and 6:1, respectively; Table 2). In contrast, tolterodine and fesoterodine displayed a similar selectivity for both M_3 and M_2 receptors. In another competitive binding study, trospium was shown to be generally non-selective for the M_3 receptor over the other muscarinic receptor subtypes [15].

To date, only two large comparative studies have been performed that evaluated the differential effects of antimuscarinics compared with placebo on HR in healthy participants of an age similar to the overall OAB population (≥50 years of age) [31, 32]. Both were three-way crossover, placebo-controlled, randomized double-blind studies comparing the HR effects of at least 7 days' treatment with darifenacin 15 mg or tolterodine 4 mg once daily. These head-to-head studies confirmed that darifenacin does not significantly increase HR (Fig. 3a) or decrease HRV over 24 h compared with placebo [31, 32]. In contrast, tolterodine significantly increased HR (Fig. 3b) and reduced HRV compared with both darifenacin and placebo.

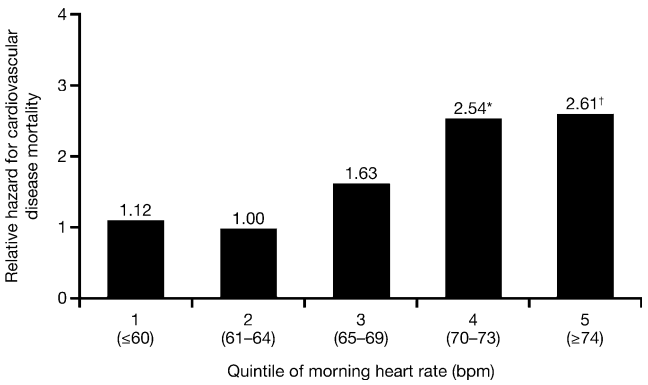

Fig. 4 Increased heart rate is associated with increased risk of cardiovascular disease mortality [85]. *$p<0.05$; †$p<0.01$ for increased risk of cardiovascular mortality vs. risk ratio of 1.0. Relative hazards were calculated by Cox proportional hazard model and adjusted for variables. *bpm* beats per minute

Mean HR increased with tolterodine by 1.84–2.24 bpm over 24 h compared with darifenacin ($p \leq 0.0004$) and by 1.42–1.84 bpm compared with placebo ($p \leq 0.003$) [31, 32]. Significant reductions in HRV were observed using the SDNN index (mean of the standard deviation of all the normal–normal intervals for all 5-min segments) and/or the R-MSSD (square root of the mean squared differences between adjacent normal–normal intervals) with tolterodine compared with both darifenacin ($p \leq 0.0120$) and placebo ($p \leq 0.03$) [31, 32].

A smaller placebo-controlled randomized study evaluating HRV following single doses of tolterodine ER 4 or 8 mg in healthy female volunteers (mean age 24 years) confirmed these findings [83]. Tolterodine significantly increased resting HR compared with placebo at both the 4-mg dose (by 8.6 bpm, $p=0.047$) and the 8-mg dose (by 12.2 bpm, $p=0.005$) [83]. In addition, tolterodine 8 mg significantly decreased HRV in this homogenous young patient population [83]. Similar to tolterodine, fesoterodine has been shown to increase HR by 3.3 bpm at the 4-mg/day dose and by 3.9 bpm at the 8-mg/day dose compared with 0.8 bpm with placebo [84].

The magnitude of HR effects (between 2 and 12 bpm) observed in these studies [31, 32, 83] may not seem large enough to be of particular concern in the healthy volunteers studied. However, even small (single-digit) increases in resting HR over prolonged periods have been associated with marked increases in mortality risk (5 bpm=16–17% increased mortality, $p=0.03$; Fig. 4) [77, 85]. This is of particular concern in the treatment of OAB, which often requires prolonged periods of therapy [86]. Furthermore, small changes in HR may have a greater impact in patients with an established higher risk for CV events and CV comorbidities, which will apply to a considerable proportion of the OAB population.

Considerations for use of antimuscarinic agents for the treatment of OAB in clinical practice

Antimuscarinic agents are used widely in the treatment of OAB and have demonstrated broadly comparable efficacy and good tolerability. Therefore, the selection of an appropriate antimuscarinic agent for the treatment of OAB must be considered carefully to ensure that patients receive optimal treatment tailored to their individual needs. The risk/benefit ratio for each antimuscarinic differs, and this may in part be due to their unique muscarinic receptor subtype binding profiles. This relative selectivity for receptors plays an important role in the development of adverse effects for the different antimuscarinics.

The potential impact of antimuscarinics on cognitive and cardiac function is a major concern in the treatment of OAB patients who are likely to present with CV comorbidities and other risk factors that may predispose them to the adverse cognitive and cardiac effects of antimuscarinic therapy. Considering that OAB is in general a benign condition [87], adding unnecessary CNS and CV risk to achieve therapeutic efficacy must be evaluated in view of the risk/benefit ratio, especially in older patients, and it is an important consideration in treatment choice.

After physicians have assessed the patient's health status and need for concomitant medications, the optimal approach for managing OAB should also be carefully considered, bearing in mind the patient's ability to understand and carry out the physician's instructions and their willingness to do so. Due to the persistent nature of OAB, the long-term efficacy and safety of the antimuscarinic should be taken into account. Furthermore, treatment should be tailored for individual patients to ensure minimal opportunity for adversely affecting their health-related quality of life and to reduce the potential negative interaction with concomitant medications being administered.

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