Review Article

Rationale for the Use of Anticholinergic Agents in Overactive Bladder With Regard to Central Nervous System and Cardiovascular System Side Effects

Bülent Çetinel, Bulent Onal

Department of Urology, Cerrahpasa School of Medicine Faculty, Istanbul University, Istanbul, Turkey

Purpose: Central nervous system (CNS) and cardiovascular system (CVS) side effects of anticholinergic agents used to treat overactive bladder (OAB) are underreported. Hence, this review aimed to focus on the mechanisms of CNS and CVS side effects of anticholinergic drugs used in OAB treatment, which may help urologists in planning the rationale for OAB treatment.

Materials and Methods: PubMed/MEDLINE was searched for the key words "OAB," "anticholinergics," "muscarinic receptor selectivity," "blood-brain barrier," "CNS," and "CVS side effects." Additional relevant literature was determined by examining the reference lists of articles identified through the search.

Results: CNS and CVS side effects, pharmacodynamic and pharmacokinetic properties, the metabolism of these drugs, and the clinical implications for their use in OAB are presented and discussed in this review.

Conclusions: Trospium, 5-hydroxymethyl tolterodine, darifenacin, and solifenacin seem to have favorable pharmacodynamic and pharmacokinetic properties with regard to CNS side effects, whereas the pharmacodynamic features of darifenacin, solifenacin, and oxybutynin appear to have an advantage over the other anticholinergic agents (tolterodine, fesoterodine, propiverine, and trospium) with regard to CVS side effects. To determine the real-life situation, head-to-head studies focusing especially on CNS and CVS side effects of OAB anticholinergic agents are urgently needed.

Keywords: *Anticholinergics; Cardiovascular system; Central nervous system; Muscarinic receptors; Overactive bladder*

Corresponding Author:
Bülent Çetinel
Department of Urology,
Cerrahpasa School of Medicine
Faculty, Istanbul University,
Mesa Avrupa Konakları Birinci
Kısım A6 Blok Daire 1,
Altunizade, Üsküdar, 34662,
İstanbul, Türkiye
TEL: +90-212-2338840
FAX: +90-212-2338840
E-mail: bulent.cetinel@hotmail.com

INTRODUCTION

Overactive bladder (OAB) is a benign, persistent condition characterized by various urinary symptoms, i.e., urinary urgency (being the driving symptom), 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 [1]. The mainstay of treatment of OAB is the use of anticholinergics, which exert their action by blocking the muscarinic M_3 receptors located on the bladder smooth muscle [2]. The M_3 subtype that principally mediates bladder contractions is also lo-

cated in the salivary glands, gastrointestinal smooth muscle, and ciliary and iris sphincter muscles, and the blockade of this receptor results in the common side effects of anticholinergics such as dry mouth, constipation, and blurred vision. These side effects, although widely reported, do not result in significant discontinuation rates compared with placebo [3-6]. The only exception is the use of oxybutynin ≥ 10 mg/d, which causes significantly higher discontinuation rates compared with placebo [5].

Important central nervous system (CNS) and cardiovascular system (CVS) side effects such as cognitive and memory impairment and increased heart rate have tradi-

tionally not been evaluated in anticholinergic trials, which has resulted in insufficient data reported by meta-analyses [3-5,7]. A systematic review on this subject demonstrated that most clinical trials testing anticholinergic agents for OAB neither measured nor reported CNS outcomes [8]. That systematic review concluded that more detailed standardized measurement of CNS outcomes in clinical trials was required to better inform patients and clinicians about significant CNS side effects.

Adherence to drug therapy in OAB has been shown to be as low as 20% after 6 months of follow-up in real-life practice [9]. In a review article it was stated that most clinical trials are of short duration, with intensive follow-up and incentives that encourage adherence. That review further commented that the high rate of adherence in clinical trials might not be representative of real-life practice [10]. It was stated that anticholinergic side effects, including cognitive impairment, comorbidity, and polypharmacy, are well-recognized factors responsible for discontinuation of drug therapy.

A cohort study demonstrated that the risk of CNS side effects increased more than twofold in elderly people who used anticholinergic drugs more than once per day compared with those who did not use anticholinergics [11].

The process of rational use of a drug treatment first starts with carefully defining the patient's problem (the diagnosis); next, specifying the therapeutic objective; then, choosing a treatment of proven efficacy and safety from different alternatives; and last, starting the treatment [12]. Although anticholinergic agents are efficacious, safe, and well-tolerated treatments for OAB, CNS and CVS side effects have not been sufficiently evaluated [3-5]. Hence, this review aimed to focus on the mechanisms of the CNS and CVS side effects of these drugs, which may help urologists in planning the rationale for OAB treatment. CNS and CVS side effects, pharmacodynamic and pharmacokinetic properties, the metabolism of these drugs, and the clinical implications for their use in OAB are discussed in this review.

CNS SIDE EFFECTS ASSOCIATED WITH OAB ANTICHOLINERGIC DRUGS

The most common CNS side effects of OAB anticholinergic agents are headache, dizziness, somnolence, confusion, and fatigue. However, more serious side effects such as memory impairment, psychotic behavior, insomnia, hallucination, and delirium can also occur [13-17]. In a recent meta-analysis reviewing the adverse events of OAB drugs, CNS adverse events were reported to be rare, and the overall CNS adverse event rates for the majority of anticholinergic agents were found to be similar to placebo [5]. However, as demonstrated in a systematic review, specific cognitive testing was not performed in most of the clinical trials, and CNS side effects were evaluated according to subjective reporting [8,13]. Subjective reporting of CNS adverse effects was shown to be unreliable because elderly patients might be unaware of the change or assume it was the

result of aging and not a drug effect [13]. Furthermore, elderly patients with preexisting cognitive impairment and comorbidity who used other medications with anticholinergic effects were often excluded from clinical trials [5,13,18]. Therefore, the incidence of CNS effects may have been underreported.

Among the anticholinergic agents, oral oxybutynin has been shown to be significantly associated with greater withdrawal rates and to have the worst adverse effect profile [3,5,13]. Oral oxybutynin use in both immediate release and extended release (ER) forms results in negative effects in cognitive function, electroencephalogram (EEG) findings, and rapid eye movement (REM) parameters and memory loss in specific objective, cognitive, and memory testings [18-22]. Psychotic behavior and hallucinations induced by oxybutynin have also been reported [23]. As a result of these data, the U.S. Food and Drug Administration (FDA) changed the oxybutynin product label in 2008 to include the potential for serious CNS side effects [13].

Although no cognitive or memory impairment in elderly and no significant quantitative EEG changes in young healthy men due to tolterodine use were reported, disorders of REM sleep parameters and several case reports of serious confusion and delirium after tolterodine use have been reported [15-17,21,22,24,25].

Several double-blind placebo-controlled trials of darifenacin confirmed that it did not negatively affect cognitive and memory function in the elderly, and it did not result in negative EEG changes in healthy young men [18,26,27].

Data from multicenter, randomized, and placebo-controlled trials of trospium chloride in elderly patients demonstrated its efficacy with no reports of CNS side effects [28]. Trospium was not detected in the cerebrospinal fluid of elderly patients taking once-daily trospium chloride ER, 60 mg, for 10 days [29]. These patients had no significant changes on standardized memory testing. Furthermore, trospium use also had no effect on REM sleep and did not change the EEG pattern [20-22].

Data regarding CNS side effects due to solifenacin use are limited. A study with a small number of healthy elderly people reported no cognitive impairment after a single 10-mg dose of solifenacin, with results similar to placebo [30].

In a randomized, double-blind study that evaluated the general safety of tolterodine, propiverine, oxybutynin, and trospium chloride compared with placebo in healthy volunteers, it was shown that tolterodine, propiverine, and oxybutynin led to impairment in tests of accuracy of perception, concentration, and vigilance, whereas trospium chloride did not [31]. To our knowledge, no study has specifically focused on the CNS side effects of fesoterodine in elderly patients with OAB.

Several factors that play a role in the CNS side effects of OAB anticholinergic agents are an increase in their plasma levels as the result of polypharmacy, properties of crossing the blood-brain barrier (BBB), anticholinergic activities in the brain, muscarinic receptor affinities, enzyme

defects, drug interactions influencing their metabolism, and preexisting CNS comorbidities.

BRAIN DISTRIBUTION (PHARMACOKINETICS) OF ANTICHOLINERGIC AGENTS: BBB

The BBB comprises brain capillary endothelial cells; a basal membrane and extracellular matrix surrounding the endothelial cells, pericytes, and astroglial processes; and tight junctions between the endothelial cells [32]. This barrier prevents most substances from entering the brain [33]. Small anticholinergic agents that are lipophilic and with neutral charge can easily cross the BBB. Oxybutynin, a tertiary amine, has all of these properties and can readily penetrate the BBB [34]. All other anticholinergic agents other than trospium are also lipophilic tertiary amines and partially unpolarized. Unlike oxybutynin, however, tolterodine, fesoterodine, solifenacin, and darifenacin are large molecules, which makes their CNS penetration more difficult [32]. On the other hand, trospium, a quaternary amine, is a large, positively charged, and hydrophilic molecule that does not readily cross the BBB [35,36].

Another component of the barrier function of the BBB is the presence of efflux transporters on the luminal and abluminal membranes of the cerebral endothelial cells [13,14]. These transport systems function to actively pump substances from the cerebral capillaries back into the systemic circulation [37]. P-glycoprotein (P-gp), the best studied efflux transporter, appears to actively pump darifenacin, trospium, and 5-hydroxymethyl tolterodine (5-HMT) from the cerebral vasculature back into the systemic circulation [13,14,32,38,39]. Oxybutynin, solifenacin, and tolterodine are not P-gp substrates, and once past the BBB, they cannot be pumped back into the systemic circulation [38].

In summary, small anticholinergic agents that have low molecular weight, are lipophilic, and have neutral charge properties and that are not P-gp substrates easily penetrate into the CNS. Consequently, the BBB is most easily crossed by oxybutynin. In normal circumstances, trospium does not appear to penetrate into the CNS. Darifenacin and 5-HMT, being P-gp substrates, do not easily cross the BBB. The pharmacokinetic properties of the anticholinergic drugs are shown in Table 1.

Some conditions, such as multiple sclerosis, type 2 diabetes mellitus, Parkinson disease, cerebrovascular disease, advancing age, and Alzheimer disease, can impair the function of the BBB and increase its permeability [13,32].

In such conditions, all anticholinergic agents used to treat OAB can cross the less-selective BBB [13]. Additionally, the cognitive function of patients with the above-mentioned progressive neurological disorders continues to decline throughout the disease course. Hence, when using anticholinergic agents in these patients, the physician must be more careful about the CNS side effects of these drugs. There are a limited number of studies evaluating the CNS side effects of anticholinergics in patients with neurogenic OAB [7]. A recent meta-analysis evaluating the anticholinergic agents for adult neurogenic detrusor overactivity concluded that compared with placebo, anticholinergic treatment was associated with better patient-reported cure or improvement, although there was a higher incidence of adverse events, such as dry mouth [40]. Interestingly, none of the 10 randomized controlled trials included in this meta-analysis mentioned the CNS side effects of these drugs, which must be evaluated in future studies.

PHARMACODYNAMICS OF ANTICHOLINERGIC AGENTS

1. Brain anticholinergic activities
Anticholinergic agents, once past the BBB, exert their CNS side effects in parallel to their affinities for muscarinic receptors located in the brain. Information about the relative pharmacodynamic potentials of different anticholinergic agents to cause CNS side effects may assist in drug selection in vulnerable patients, such as patients with neurogenic bladder and elderly patients with many comorbidities. A recent study compared the central pharmacodynamic potentials (brain anticholinergic activities) of five different anticholinergic agents (tolterodine, darifenacin, solifenacin, oxybutynin, and fesoterodine) by using a small-sample, high-throughput version of the anticholinergic radio receptor bioassay method [41]. The principle of the method was based on measuring the specific binding of tritiated quinuclidinyl benzilate (3H-QNB) to rat brain muscarinic receptors in the presence of serum. Substances with affinity for muscarinic receptors inhibited binding of 3H-QNB, and the degree of displacement reflected the anticholinergic activity in serum with the use of atropine as a reference compound [42]. The authors concluded that tolterodine and fesoterodine appeared to have the highest pharmacodynamic potential to induce CNS side effects, whereas darifenacin and solifenacin displayed low brain anticholinergic activ-

TABLE 1. Pharmacokinetic properties of anticholinergic drugs

Property	Oxybutynin	Tolterodine	Trospium	Propiverine	Solifenacin	Darifenacin	Fesoterodine
Molecular weight	Small	Large	Large	Small	Large	Large	Large
Lipophilicity	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	Lipophilic	Lipophilic	Lipophilic
Charge	Neutral	Positive	Positive			Positive	Positive
P-gp substrate	No	No	Yes	No	No	Yes	Yes

P-gp, P-glycoprotein.

ities with low clinical potential to induce cognitive side effects. In that study, the anticholinergic activity of oxybutynin was not particularly high at lower therapeutic concentrations, but was nearly 5 times as high in the upper part of the concentration range. This finding was consistent with a previous study in which oxybutynin 5 mg daily was not associated with a greater risk of side effects than placebo in cognitively impaired nursing home residents [43].

Consistent with the data from this recent study, another former study found that the brain anticholinergic activity of tolterodine was several times as high as that of oxybutynin at high serum concentrations [44]. *In vitro* findings from these two studies support the clinical findings that oxybutynin and tolterodine cause significant CNS side effects, whereas solifenacin and more prominently darifenacin do not usually impair cognitive function [15-27,30,45].

2. Muscarinic subtype selectivity

Five distinct muscarinic receptor subtypes (M1–M5) are distributed throughout the body mediating distinct physiological functions according to their location and receptor subtype [2]. Although all five muscarinic receptors have been determined in the brain, M_1 and M_2 receptors are considered to play an important role in memory and cognitive function [2,7]. Blockade of especially central M_1 receptors was thought to have an important role in cognitive impairment. Consequently, anticholinergic agents with affinity for this receptor subtype may be associated with CNS side effects, but the pharmacokinetic properties of anticholinergics must also be taken into account [2,7]. Darifenacin demonstrated the highest selectivity of 16:1 for the M_3 receptor over the M_1 subtype in a competitive binding study, whereas solifenacin had a moderate selectivity of 2:1. All other anticholinergic agents (tolterodine, oxybutynin, trospium, propiverine, and fesoterodine) were found to be nonselective for the M_3 receptor over the M_1 subtype [7,46,47]. Darifenacin had the highest selectivity for the M_3 receptor over the M_2 subtype, whereas solifenacin and oxybutynin had moderate selectivity. The other anticholinergic agents (tolterodine, trospium, propiverine, and fesoterodine) were found to be nonselective for the M_3 receptor over the M_2 subtype [7,46,47]. Table 2 summarizes the relative muscarinic subtype selectivity of anticholinergic agents.

METABOLISM OF ANTICHOLINERGIC AGENTS

Most side effects of anticholinergic agents are linked to their mechanism of action and metabolism. Hence, urologists must be familiar with these features of OAB drugs for better understanding of CNS and CVS side effects. All of the currently used oral OAB anticholinergic agents (except trospium) are metabolized largely in the gut wall and the liver by first-pass metabolism [48]. They are excreted by the kidneys in active or inactive forms in varying proportions.

Darifenacin is mainly metabolized by CYP2D6 and 3A4 in the liver, and renal clearance is negligible [48]. No dose adjustment but cautious use is recommended in renal failure [49,50]. Darifenacin is not recommended in severe hepatic failure, with cautious use in mild and moderate hepatic failure [49,50]. Both *fesoterodine* and *tolterodine* are converted to the active metabolite 5-HMT by nonspecific esterases and the CYP2D6 enzyme system, respectively [51]. 5-HMT in turn is metabolized in the liver by CYP2D6 and 3A4, yielding inactive secondary metabolites, and is partly cleared by the kidneys [51]. Fesoterodine and tolterodine should be used with caution in mild and moderate hepatic failure and are not recommended in severe hepatic failure [52,53]. Cautious use of both fesoterodine and tolterodine is advised in mild and moderate renal impairment, with recommendation of a maximum fesoterodine dose of 4 mg/day and tolterodine dose of 2 mg/d in severe renal failure [52,53].

Oxybutynin is metabolized in the liver by CYP3A4 to its active metabolite, N-desethyloxybutynin. Many of the anticholinergic adverse effects observed after oral dosing of oxybutynin seem to be secondary to high circulating levels of its active metabolite, N-desethyloxybutynin [54]. Because CYP3A4 is found only in small amounts in the skin, transdermal application of oxybutynin offers the advantage of less systemic side effects [54]. Although no studies are available, caution is advised when using oxybutynin in hepatic and renal failure [55].

Propiverine is primarily metabolized by CYP3A4 and flavin monooxygenases. Because serum levels of the parent compound and its main weakly active metabolite propiverine-N-oxide are not significantly changed by severe renal impairment, no dosing adjustment is recommended [56]. Although no advice on dose adjustment is given in the package inserts for hepatic failure, caution should be exercised in this situation.

Solifenacin is primarily metabolized by CYP3A4 in the liver and is partly excreted by the kidneys. Solifenacin should be used with caution in renal and hepatic failure [57].

Trospium is a hydrophilic quaternary amine and does not undergo major metabolism but rather is largely cleared by the kidneys in active form [48]. It should be used with caution in hepatic failure with no dose adjustment [58]. In patients with renal failure, dose reduction to 20 mg per 2

TABLE 2. Relative muscarinic subtype selectivity of anticholinergic agents

Anticholinergic agent	M_3 vs. M_1 selectivity	M_3 vs. M_2 selectivity
Darifenacin	High	High
Solifenacin	Moderate	Moderate
Oxybutynin	None	Moderate
Fesoterodine	None	None
Tolterodine	None	None
Trospium	None	None
Propiverine	None	None

days should be made [58]. The renal excretion and hepatic metabolism of anticholinergic agents are summarized in Table 3.

Approximately 7% to 10% of whites are genetically deficient in CYP2D6 (poor metabolizers), which can lead to elevated serum levels of drugs that are metabolized by that enzyme (darifenacin, fesoterodine, and tolterodine) [13,48]. Tolterodine-treated individuals with the poor metabolizer phenotype have considerably higher tolterodine and low or even undetectable 5-HMT plasma concentrations [48]. Tolterodine is not a P-gp substrate and has greater brain penetration than does 5-HMT [37]. In a recent study it was demonstrated that tolterodine appears to have the highest and darifenacin the lowest brain anticholinergic activity and pharmacodynamic potential to induce central anticholinergic side effects of the tested anticholinergic agents [41]. All of these findings correlate well with clinical studies relating to disorders of REM sleep parameters and several case reports of serious confusion and delirium after tolterodine use [15-17,24,25]. These data show that tolterodine-treated patients with the poor metabolizer phenotype may have a high risk of developing CNS side effects. Although darifenacin metabolism was also effective in poor metabolizers, because darifenacin was shown to be a P-gp substrate and to have lower brain penetration and no negative effects on cognitive or memory function in the elderly [18,26,27], the risk of CNS side effects in darifena-

cin-treated patients with the poor metabolizer phenotype did not seem to be high.

Coadministration of medications affecting the activity of CYP2D6 or 3A4 can give rise to important drug–drug interactions. Potent CYP2D6 inhibitors are bupropion, fluoxetine, paroxetine, terbinafine, quinidine, and cimetidine, whereas clinically relevant CYP3A4 inhibitors include ritonavir, ketoconazole, itraconazole, verapamil, cyclosporine, erythromycin, clarithromycin, fluconazole, and grapefruit juice [48]. Patients with the poor metabolizer phenotype are particularly at risk for drug interactions with CYP2D6 inhibitors [48]. A thorough patient history regarding comedications will help the urologist to tailor the OAB medication to an individual patient.

POLYPHARMACY IN THE ELDERLY

The prevalence of OAB increases with age [59]. Elderly people are often administered many concomitant medications for a variety of other conditions, including those relating to cognitive and cardiac function. Many commonly used drugs in the elderly, such as antiparkinsonian agents, antidepressants, antihistamines, antiemetics, antipsychotics, muscle relaxants, and antivertigo, cardiovascular, and gastrointestinal agents, have anticholinergic properties [11] (Table 4).

It was shown that more than 30% of nursing home resi-

TABLE 3. Renal excretion and hepatic metabolism of anticholinergic agents

Anticholinergic	Renal excretion	Hepatic metabolism
Trospium	Mainly as unchanged	No hepatic metabolism
Oxybutynin	Negligible	CYP 3A4
Tolterodine	Negligible as tolterodine, partly as 5-HMT	CYP 2D6 generates 5-HMT 5-HMT metabolized by CYP 2D6, CYP 3A4
Fesoterodine	Partly	5-HMT metabolized by CYP 2D6, CYP 3A4
Propiverine	Negligible	CYP 3A4 and flavin monoxygenases
Darifenacin	Negligible	CYP 2D6 and 3A4
Solifenacin	Partly	CYP 3A4

5-HMT, 5-hydroxymethyl tolterodine.

TABLE 4. Drugs with anticholinergic properties (OAB drugs excluded)

Category	
Antihistamines	Chlorpheniramine, cyproheptadine, diphenhydramine hydroxyzine
Antidepressants	Amoxapine amitriptyline clomipramine desipramine doxepin Imipramine nortriptyline protriptyline paroxetine
Antiemetics	Prochlorperazine promethazine
Antipsychotics	Chlorpromazine clozapine olanzapine thioridazine
Antivertigo	Meclizine scopolamine
Cardiovascular	Furosemide digoxin nifedipine disopyramide
Gastrointestinal	Diphenoxylate atropine clidinium chlordiazepoxide Dicyclomine hyoscyamine propantheline cimetidine ranitidine
Muscle relaxants	Cyclobenzaprine dantrolene orphenadrine
Anti-Parkinson	Amantadine benztropine biperiden trihexyphenidyl

OAB, overactive bladder.

dents in the United States took three or more drugs with anticholinergic properties, and 5% took more than five such medications [60,61]. Increased anticholinergic load, potential drug–drug interactions resulting from polypharmacy, age-related decline in cholinergic function, and impaired function of the BBB make elderly people more vulnerable to the CNS side effects of anticholinergic agents [13,33,62].

Although the efficacies of OAB anticholinergic agents have been shown to be the same, accumulating evidence indicates that the potential for the different anticholinergic drugs to adversely affect cognitive function varies from agent to agent [3,4,7]. Hence, when selecting a specific antimuscarinic agent for an individual elderly OAB patient, the urologist after taking a thorough patient history regarding comedications must choose the appropriate anticholinergic agent with low potential to induce CNS side effects. If possible, the anticholinergic load of the patient must be decreased. A thorough patient history is also required to avoid prescribing agents with potential drug–drug interactions. For example, it may be possible to avoid the coadministration of anticholinergics for OAB therapy with cholinesterase inhibitors, which are typically used to improve memory and cognition in Alzheimer's disease and which have typical OAB-like side effects [13,63-65]. A population-based retrospective cohort study found that the use of cholinesterase inhibitors was associated with an increased risk of receiving an anticholinergic drug to manage urinary incontinence. The authors concluded that clinicians should consider the possible contributing role of cholinesterase inhibitors in new onset or worsening urinary incontinence and the potential risk of coprescribing cholinesterase inhibitors and anticholinergic drugs to patients with dementia [63]. On the contrary, chronic use of OAB anticholinergic agents may result in a pharmacodynamically induced Alzheimer disease state [13].

PREEXISTING CNS COMORBIDITIES

A recent study utilizing the national Electronic Medical Record database to identify OAB patients found that 45.4% of the patients with OAB had preexisting CNS conditions at baseline, a significantly higher proportion than the 29.0% of non-OAB patients with the same CNS conditions [66]. Another important finding of that study was that a higher proportion of the treated OAB patients had preexisting syncope and dizziness than was the case among untreated OAB patients [66]. These findings from real-life settings show clearly that antimuscarinic medications with strong CNS side effect profiles can potentially worsen these preexisting comorbidities.

CARDIOVASCULAR SAFETY AND SIDE EFFECTS

Although M_2 receptors dominate M_3 receptors in the bladder in a 3:1 ratio, M_3 receptors seem to be the most important muscarinic receptors for detrusor contraction [2,67]. M_2 receptors located in the bladder may play a role in detrusor contraction by reversing β-adrenoceptor-mediated smooth muscle relaxation, indirectly enhancing M_3 receptor mediated contractions, or increasing urgency sensations [68-71].

The M_2 receptors are also located in heart and modulate heart pacemaker activity and atrioventricular conduction. The blockage of M_2 receptors, in addition to the inhibitory effect on detrusor contraction through M_3 pathways, also results in an increase in heart rate [72].

Antimuscarinic drugs differ in their pharmacological profile at the five distinct human muscarinic receptors [73]. Tolterodine, fesoterodine, propiverine, and trospium essentially do not discriminate between the five subtypes. Oxybutynin and solifenacin do possess marginal selectivity for M_3 over the M_2/M_5 subtypes, whereas darifenacin has a high degree of selectivity for M_3 over the M_2/M_4 subtypes. Theoretically, in terms of the increase in heart rate, OAB antimuscarinics having selectivity for M_3 over M_2 must be advantageous to others with no selectivity. A review article commented on this issue that differentiating risk profiles based on pharmacokinetics, receptor selectivity, and clinical effects would be beneficial to physicians in choosing an individually optimum OAB treatment, although there were few clinical trials designed to assess the cardiovascular effects of antimuscarinics and a very limited number of head-to-head comparisons of the drugs [73].

In another review article about the pharmacodynamics of OAB drugs it was stated that it was not possible to show causal relationships between the receptor binding properties and the adverse effects of these drugs owing to the lack of clinical head-to-head studies, but general acceptance existed for such a relationship between the two [68]. In this context, darifenacin and solifenacin, which had high and moderate M_3 versus M_2 selectivity, respectively (Table 2), were found to cause dry mouth and constipation more than trospium, tolterodine, and fesoterodine, which had no M_3 versus M_2 selectivity [2,7,74]. On the other hand, darifenacin and solifenacin would be expected to have less of an effect on heart rate than trospium, tolterodine, and fesoterodine owing to lower M_2 occupancy [68]. Two randomized double-blind three-way crossover studies evaluated the differential effects of antimuscarinics (darifenacin and tolterodine) compared with placebo on heart rate in healthy participants (≥50 years of age) [75,76]. These head-to-head studies confirmed that darifenacin did not significantly increase heart rate, whereas tolterodine significantly increased it compared with both darifenacin and placebo. In an open-label, postmarketing surveillance study, it was shown that therapeutically effective doses of solifenacin (5–10 mg) did not increase heart rate [77]. Two placebo-controlled randomized studies showed that tolterodine and fesoterodine at both 4-mg and 8-mg doses significantly increased resting heart rate compared with placebo [78,79]. It has been shown that even small increases in resting heart rate over prolonged periods have been associated with marked increases in mortality risk [80]. Furthermore, in epidemiological studies, increased resting heart rate has

been linked with increased mortality, particularly in patients with cardiovascular disease [73,81,82].

In a study of adult patients with OAB, it was shown that patients with OAB were significantly more likely to have cardiovascular comorbidities than were age- and gender-matched non-OAB patients, and a large proportion (39%) of OAB patients had an elevated heart rate of ≥ 80 beats per minute before starting anticholinergic treatment [83]. The side effects of an increase in heart rate due to anticholinergic treatment of OAB have not been reported in systematic reviews and meta-analyses [3-5,84].

A recent study found that all OAB patients had a significantly higher proportion of preexisting cardiovascular disorders, such as ischemic heart disease, conduction disorders, heart failure, cardiovascular symptoms, and hypertension, than did non-OAB patients. Hypertension was the most common preexisting condition [66]. The authors concluded that comorbidities and concomitant medications affecting the CVS should be taken into account when making the decision on the most appropriate OAB treatment option for each patient.

A recent review article about the cardiovascular effects of antimuscarinic agents in OAB concluded that, although the cardiovascular safety of OAB antimuscarinic drugs seems to be good, the evidence included did not allow for the exclusion of an increase in heart rate, QT prolongation, or an increase in cardiovascular risk due to drug–drug interactions in OAB patients, particularly elderly patients with comorbidities [85]. The authors further commented that clinical and electrocardiographic monitoring might be necessary throughout the administration period in selected populations such as patients aged >80 years and those with coronary heart disease or congestive heart failure [85].

Studies evaluating the cardiovascular side effect profile of anticholinergic agents are urgently needed. Until then, the urologist must seriously consider the possibility of an increase in heart rate due to anticholinergic agents during long-term treatment of OAB. To prevent associated cardiovascular mortality, the urologist should try to choose an anticholinergic agent with low potential for increasing heart rate according to its subtype selectivity (Table 2).

CLINICAL IMPLICATIONS FOR USE OF ANTICHOLINERGIC AGENTS IN OAB

The CNS and CVS side effects of OAB anticholinergic agents are underreported. More detailed standardized measurement of CNS side effects is required to better inform patients and clinicians about the CNS risks associated with anticholinergic agents. With regard to CVS side effects, an increase in resting heart rate, which was found to be associated with increased mortality, must be evaluated with head-to-head studies of anticholinergic agents to determine the anticholinergic agents with low potential for inducing an increase in heart rate. Until such studies are available, urologists must rely on their knowledge of

the pharmacodynamics, pharmacokinetic properties, and metabolism of these drugs and in parallel with rational drug use principles must choose the appropriate anticholinergic to minimize CNS and CVS side effects.

At this moment, trospium, 5-HMT, darifenacin, and solifenacin seem to have favorable pharmacodynamic and pharmacokinetic properties with regard to CNS side effects. With regard to CVS side effects, the pharmacodynamic features of darifenacin, solifenacin, and oxybutynin appear to have an advantage over the other anticholinergic agents (tolterodine, fesoterodine, propiverine, and trospium). To determine the real-life situation, head-to-head studies focusing especially on the CNS and CVS side effects of OAB anticholinergic agents are urgently needed.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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