Antimuscarinic drugs for the treatment of overactive bladder: are they really all the same? – A comparative review of data pertaining to pharmacological and physiological aspects

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Summary

Worldwide, muscarinic antagonists are the mainstay of pharmacotherapy for the symptoms of overactive bladder. Although all currently available drugs are almost comparable with regard to their clinical efficacy, variations in the chemical structure, metabolism and receptor-ligand behaviour influence their specific side-effect profile. Therefore, the purpose of this paper is to identify and compare these pharmacological and physicochemical properties of the different antimuscarinics pertaining to their tolerance potential in relevant patient populations. Awareness of these subtle differences can help the physician to determine which of the available drugs might offer practical advantages and/or disadvantages over the others for an individual patient.

Key words


Zusammenfassung

Anticholinergika zur Behandlung der überaktiven Blase: wirklich eines wie das andere? Ein vergleichender Überblick zu pharmakologischen und physiologischen Aspekten:


Schlüsselworte

Antimuskarinika – überaktive Blase (OAB) – chemische Struktur – Metabolismus – Arzneimittelinteraktionen – Muskarinrezeptoren – ZNS-Einflüsse
The micturition reflex consists of a urine filling or storage phase which continues until afferent nerve activation signals that the bladder is sufficiently full. This is followed by an emptying phase with the controlled firing of parasympathetic efferent nerves to contract detrusor smooth muscle to initiate voiding [7, 10, 28, 51, 52]. Muscarinic receptors, which play a crucial role in detrusor muscle contraction and bladder emptying, are abundant in the human bladder [45, 46, 89]. Impaired bladder control is a frequent problem. In individuals with no detectable neurological lesions, loss of bladder control appears to be specifically related to inadequate activation of the orbitofrontal cortex, an area known to be crucial to voluntary bladder control [52]. It is not known whether the characteristic symptoms of overactive bladder (OAB)* result from increased bladder contractile activity during the storage phase and/or from increased sensitivity of the afferent limb of micturition. Nevertheless, it is well established that the synaptic release of acetylcholine (ACh) from activated parasympathetic nerves and subsequent binding of ACh to muscarinic (M) receptors is the central mechanism in normal voiding contractions as well as in involuntary bladder contractions [5, 7, 8, 32, 36, 62, 135]. Antimuscarinics (muscarinic receptor antagonists) are competitive antagonists that reversibly block post-synaptic excitatory muscarinic receptors (M3/M4). They exert their favourable effects on detrusor muscle mainly during the storage phase when there is normally no excitatory parasympathetic input to the lower urinary tract; they thereby abolish or reduce detrusor muscle contractility, increase bladder capacity and in turn, improve the primary clinical symptoms of OAB [5, 7, 8, 31, 32, 36, 59, 62]. With the OAB-specific antimuscarinics, urge incontinence episodes usually decrease by 70 to 75%, micturition frequency may decrease by 20 to 30%, and the volume voided may increase by 10 to 20%, [135]. Since antimuscarinics are usually competitive antagonists, their effects should theoretically be lower when there is a massive release of ACCh such as that which occurs during micturition [5, 8]. Treatment of OAB with anticholinergics is therefore logistical and rational, and these drugs are regarded as the cornerstone of OAB pharmacotherapy [5, 7, 36, 62, 107].

The ideal antimuscarinic agent for treatment of OAB would be one that: (1) is 100%, bladder selective, i.e. does not affect muscarinic receptors in other organ systems; (2) eliminates bladder overactivity without impairing normal micturition; (3) lacks drug-drug interactions; (4) is extremely safe and tolerable; and (5) is easy to administer. However, this prototype drug has yet to be developed. Although the different antimuscarinic agents have been extensively studied, their exact mechanisms of action are not completely understood. Recent investigations and ongoing research appear to offer new potential targets for pharmacological intervention with antimuscarinics, which must be carefully evaluated. However, the clinical efficacy of the currently available antimuscarinics is well established and the different agents are comparable [7, 135]. The main problem with antimuscarinics is that none of these drugs selectively targets only the muscarinic receptors in the bladder: they are not tissue specific. By virtue of their mechanism of action, antimuscarinics commonly interact with muscarinic receptors throughout the body, thereby affecting a variety of physiological functions. The relatively common and well-known peripheral side effects of antimuscarinics diminish the tolerability and usefulness of these drugs [7, 31, 107, 135]. Most of these side effects (dry mouth, constipation, etc.) are mild, tolerable and/or easy to treat. However, certain antimuscarinics can cause more complex adverse effects such as blurred vision, cognitive impairment and cardiovascular disorders. The latter are a major limitation of existing antimuscarinics because they are more difficult to recognise and treat. Elderly patients, who comprise the predominant proportion of the relevant patient population, are the most susceptible [69, 70, 80, 137]. Antimuscarinic side effects frequently force patients to discontinue treatment, leaving their OAB symptoms unmanaged.

OAB is a common yet disabling condition with a considerable negative impact on the patient’s quality of life, quality of sleep and mental health [72, 87, 128, 136, 137]. OAB affects more than 50 million people in the developed world [7]; its socioeconomic impact is therefore profound [56, 72, 87, 107, 136-138]. Although OAB can affect anyone at any age, the prevalence of the disease tends to increase with age, irrespective of gender: 30–60%, of patients are over 65 years of age [13, 55, 72, 97, 107, 135-138]. In view of the changing age structure of the population, the importance of OAB and of suitable (pharmaco)therapies are becoming more and more relevant. Any drug used to treat the geriatric patient must be very sensitive: numerous non-urinary pathological, anatomical, physiological and pharmacological factors contribute to the development of OAB [137]. Many factors outside the lower urinary tract may also affect the feasibility and efficacy of OAB therapy.

Consequently, a sound knowledge of physiological and pathological processes in the bladder, of the physicochemical and pharmacokinetic properties of the relevant antimuscarinics, and of differences in receptor-ligand behaviour can help the physician to determine which of the available drugs might offer advantages over the others for an individual patient with the objective of designing an individualised, well tolerated and most effective treatment plan.

*The term overactive bladder (OAB) is used in this article according to the recommendations of the International Continence Society (ICS) [2, 3, 120, 133]
METHODS

Computerised library systems such as Medline, BIOSIS and EMBASE were analysed regarding data on the chemical structure, metabolism and receptor-ligand behaviour of the antimuscarinic drugs currently used for OAB. We carefully considered excluding data on clinical efficacy studies because such data have already been reviewed and evaluated extensively, thereby confirming the comparable clinical efficacy of these drugs. Moreover, due to their design, studies on efficacy are mostly unsuited for the assessment of pharmacological and specific safety questions.

STRUCTURAL DIFFERENCES BETWEEN ANTICHOLINERGICS

Basic drug chemistry

The currently available antimuscarinics can generally be typed as either tertiary or quaternary amines, i.e. as ammonia derivatives created by substitution of three or four hydrogen atoms with alkyl or aryl groups [7, 36, 53, 56, 62]. A tertiary amine has three substitutions, a quaternary amine has four. Like the naturally-occurring alkaloids atropine and hyoscine, the older antimuscarinic drugs oxybutynin chloride, propiverine hydrochloride and tolterodine tartrate, and the novel antimuscarinics darifenacin and solifenacin are tertiary amines, whereas the antimuscarinics propantheline bromide and trospium chloride are quaternary amines [7, 53]. These differences in molecular structure give rise to physicochemical and pharmacokinetic differences.

Generally, tertiary amines are highly lipophilic molecules that can easily penetrate cell membranes [7, 53] (Fig. 1). Lipophilia promotes absorption of these compounds from the gut. Theoretically, it may also enable them to cross the blood-brain barrier (BBB) by passive permeation, which could lead to central nervous system (CNS) side effects. In quaternary ammonium compounds, the replacement of four hydrogen atoms with alkyl or aryl groups confers a positive charge to the molecules and makes them highly hydrophilic, thus decreasing their ability to cross cell membranes by diffusion. Consequently, trospium chloride, as a quaternary amine, has a relatively low and slow rate of intestinal absorption and a highly restricted ability to passively penetrate through lipid cell membranes [7, 53].

FUNCTIONAL DIFFERENCES BETWEEN ANTICHOLINERGICS

Metabolism and drug interactions

Extensive first-pass metabolism following oral administration is another parameter by which the currently used antimuscarinic drugs can be compared and differentiated [53]. All tertiary amines used to treat OAB are metabolised by the hepatic cytochrome P450 system into active and/or inactive metabolites (Table I). The most commonly involved P450 enzymes are CYP2D6 and CYP3A4. In the case of oxybutynin, tolterodine, propiverine and darifenacin, a number of inactive metabolites as well as major active metabolites with a pharmacological profile similar to that of the parent compound are formed [1, 25, 26, 57, 96, 100, 125, 134]. It is therefore reasonable to assume that the clinical efficacy of these drugs is to a large extent due to the metabolites. Metabolic conversion increases the risk of drug-drug interactions and results in reduced (enzyme induction) or increased (enzyme inhibition, substrate competition) plasma concentrations of the antimuscarinic and/or interacting drug [7].

In contrast, trospium chloride, a quaternary amine, does not undergo biotransformation during absorption or first-pass hepatic extraction or extensive metabolism [43, 53]. Approximately 9–10 %, of the oral trospium dose is absorbed, and approximately 70–80 %, of the absorbed fraction is excreted in unchanged form via the urine within 48 h [43, 111, 112]. In vitro studies indicate that metabolism of trospium is minor, and that no active metabolites are produced [43, 81–83]. In clinically relevant doses, the drug is not degraded by human esterases in serum or plasma [81]. Trospium chloride is remarkably resistant to human cytochrome P450-induced metabolism [82, 83]. Consequently, the pharmacologically active drug is present in human urine and it may have local effects in the bladder during the storage phase in addition to its systemic effects. In a recent study, human urine collected from two volunteers who had taken clinically relevant oral doses of trospium, tolterodine and oxybutynin, respectively, for 5 days was instilled into the bladders of rats [76, 77]. The investigators found that trospium prevented carbachol-induced reduction of bladder capacity and inter-contraction intervals,
but oxybutynin or tolterodine did not. None of the drugs led to a change in maximum voiding pressure or pressure thresholds. These data suggest that if pharmacologically relevant doses of antimuscarinic drugs or their active metabolite(s) are excreted via the urine following oral administration, then these agents might be able to suppress bladder overactivity by locally inhibiting muscarinic receptors in the urothelium and/or suburothelial sensory structures [77].

Although metabolism of trospium by the cytochrome P450 system is negligible, the drug may theoretically affect the activity of these important rate-limiting drug-metabolising enzymes, giving rise to metabolic drug-drug interactions. Metabolic interactions may occur with drugs that share the same metabolic pathway, e.g. the same cytochrome P450 isoenzymes, and they may occur with drugs that are not substrates for a given enzyme but increase or inhibit its activity. This may lead to a corresponding increase or decrease in the serum concentration of the parent drug. The intensity of anticholinergic effects and side effects varies depending on the type of metabolite formed (active or inactive). In the case of the highly metabolised amines oxybutynin, tolterodine, propiverine and darifenacin, potential metabolic interactions with a number of drugs that interfere with these enzymes cannot be excluded. In the case of darifenacin, concomitant use of CYP3A4 inhibitors such as ketoconazole and erythromycin increases the bioavailability of darifenacin from 15–25 %, to approximately 100 %, and 97 %, respectively [73]. An interaction potential also exists for tolterodine and potent inhibitors of this isoenzyme in patients with deficient CYP2D6 activity [25]. In vitro data on the inhibitory effect of trospium on the activity of the seven most important human cytochrome P450 isoenzymes in human liver microsomes showed that trospium inhibited CYP2D6 enzymes, but only at concentrations three times higher than the maximum plasma drug concentration after standard oral dosage in humans [11]. CYP2D6 is responsible for metabolising a number of drugs, including tricyclic antidepressants and some antipsychotics and beta-adrenoceptor antagonists. Inhibition of this enzyme can potentially cause drug interactions, particularly in elderly patients who generally have an increased frequency of co-medications. However, the risk of such interactions with trospium in therapeutic practice does not seem to be relevant.

**Affinity of antimuscarinics to muscarinic receptor subtypes**

Muscarinic receptors are found in three locations in the human urinary bladder: detrusor muscle, mucosa and presynaptic regions.

**Detrusor muscle muscarinic receptors**

Radioligand binding, molecular, immunological and functional studies consistently indicate that the majority of M3 receptors (~71 %) and smaller populations of M1 (~22 %) and M4 (~7 %) receptors are present in the human detrusor [46, 61, 89]. Molecular studies also detected a small population of M5 receptors in the bladder [89]. Although it is generally accepted that the M3 receptor subtype mainly mediates cholinergic activation of the normal human urinary bladder, this fact is again currently under debate [108]. However, functional experiments in M3 knockout mice [94] and in isolated human detrusor strips [34, 47] have indicated that the M3 receptor probably has a greater impact on normal micturition contraction than the M2 receptor. The M3 receptor is thought to cause direct detrusor smooth muscle contractions by a mechanism that relies on the entry of extracellular calcium through L-type channels and activation of a rho kinase [110] (Fig. 2). Inversely, activation of the dominant M2 receptor during micturition involves inhibition of the sympathetically evoked (via beta3-adrenoceptors) detrusor relaxation through opposing effects on intracellular cAMP levels, thus resulting in more efficient initiation of voiding and bladder emptying [8, 32, 33, 50, 60, 61, 93, 141, 142]. M3 and beta-adrenoceptors counteract each other via adenylyl cyclase activity [50]. In addition, it has been suggested that the rela-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tertiary structure</th>
<th>Quaternary structure</th>
<th>Metabolising enzyme</th>
<th>Active metabolites</th>
<th>Metabolic drug-drug interactions</th>
<th>Active compound (urine)</th>
</tr>
</thead>
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<tr>
<td>Oxybutynin</td>
<td>[1, 53, 64, 96]</td>
<td>X</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>Yes</td>
<td>Very low</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>[25, 26, 53, 106]</td>
<td>X</td>
<td>CYP2D6 (CYP3A4)</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt; 1 %</td>
</tr>
<tr>
<td>Propiverine</td>
<td>[57, 125]</td>
<td>X</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>[78, 116, 122]</td>
<td>X</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>Yes</td>
<td>11 %</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>[73, 114]</td>
<td>X</td>
<td>CYP3A4</td>
<td>Yes</td>
<td>Yes</td>
<td>~ 3 %</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>[11, 43, 81-83, 111, 112]</td>
<td>X</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>75 %</td>
</tr>
</tbody>
</table>

Table 1: Comparison of drug metabolism.
Noradrenaline [51, 52, 59, 62] In myofibroblasts-like cells, M2 and M3 receptors have been implicated as a main cause of OAB [8, 32, 36]. Abnormal activation of muscarinic receptors in the human bladder has been associated with detrusor overactivity [5, 32, 45, 59, 62, 130]. Furthermore, investigations in patients with neurogenic bladder dysfunction and in certain organ transplant donors showed that the contraction-mediating muscarinic receptor subtype shifts from predominantly M3 to M2 [22, 105] or to a combination of M2 and M3, as was found to occur in the denervated hypertrophied rat bladder [16–20, 23]. Recent results in hypertrophied rat bladders indicated that changes in mRNA concentrations correlate directly with changes in M3 receptor protein density, whereas no correlation exists between M2 receptor density and M3 receptor transcripts [21]. Therefore, direct extrapolation of transcript density to protein density and thus to functional effects is probably inaccurate. The functional role of the changing receptor densities is an open question at the moment.

Mucosal muscarinic receptors

The mucosa was once thought to be a passive membrane. However, recent investigations have revealed that the mucosa (urothelium and lamina propria) participates actively in sensory functions (i.e., ability to express a number of sensor molecules or respond to thermal, mechanical, and chemical stimuli) and can release chemical mediators [6, 14, 37]. Radioligand binding and molecular studies demonstrated a significant population of M2 receptors (~75%) and minor populations of M3, M1 and M5 in the human urinary bladder mucosa [74, 89, 91, 98]. Afferent sensory nerves were localised next to the urothelium forming a plexus that penetrates the basal lamina and enters the basal urothelial cell layer [6, 14, 37, 49, 74]. Urothelial cells can respond to different stimuli by releasing a number of substances, including ACh [143, 145, 146], ATP [49] and other mediators [6, 15, 29, 74], which may stimulate or inhibit contraction of the underlying detrusor smooth muscle [14]. As the urothelium is not cholinergically innervated, ACh may act in an autocrine fashion in this tissue to modulate contractility [33, 45, 49, 144]. The presence of urothelium-derived release of transmitters, the high density of mainly M2 muscarinic receptors in the mucosa and their anatomical juxtaposition with afferent sensory nerves raises the question of the physiological significance of the mucosa. Current opinion is that the urothelium and suburothelial sensory structures influence the complex transduction process underlying the threshold for bladder contraction by converting mechanical stimuli (bladder stretch) to a cascade of afferent potentials that regulate bladder sensory functions during bladder filling [6, 49].

**Fig. 2. Effects of M2 and M3 receptors on contraction and relaxation of the detrusor muscle (→ promoting effect, — inhibiting effect).**
factors may exert their effects directly on afferent endings (ATP via P2X3 receptors), thus altering excitability; they may also take effect indirectly via myofibroblasts [37, 49], which may modulate afferent activity via communication with the urothelium, afferent nerve endings and detrusor smooth muscle. In summary, certain sensory receptors relay messages between the urothelium and afferent nerves and between the urothelium and detrusor smooth muscle. Antimuscarinics also act to inhibit these receptors.

However, there is only indirect experimental evidence for non-neuronal, urothelial ACh today. Yoshida et al. [144, 146] measured ACh release from isolated human bladder strips and demonstrated reduced release in preparations when the epithelium had been removed. These findings are compatible with the urothelial release of ACh, but also with urothelial release of another factor that might trigger ACh release from deeper structures [84]. Yoshida et al. [143] also found significant positive correlations between age and purinergic neurotransmissions, and significant negative correlations between age and cholinergic neurotransmissions in isolated human bladder smooth muscle specimens. Smooth muscle stretching also affected ACh release [145]. Recent investigations support these results, finding a significant age-related and stretch-induced increase in non-nerve evoked ACh release [144]. This suggests that the non-neuronal cholinergic system may contribute to the physiology of human bladder function. Immunohistochemical staining of isolated mouse and human urothelium with an antibody against choline acetyltransferase (ChAT), the classical ACh synthesis enzyme, indicated the presence of immunoreactive cells [79, 84]. RT-PCR data support the presence of carnitine acetyltransferase (CarAT)-mRNA, another ACh-synthesising enzyme, but not of ChAT-mRNA. These data imply that urothelial ACh may be generated either from CarAT or from an as yet unidentified variant of ChAT; another possibility is that urothelial ACh was originally neuronal ACh that was released from afferent nerves of the subepithelial plexus and transported to the urothelium [79, 84]. The human vesicular ACh transporter (VACht) shuffling ACh from the cytosol into synaptic vesicles in cholinergic neurons was detected in subepithelial cholinergic nerve fibres, but not in the urothelium. The latter itself expresses organic cation transporters (OCT1 and OCT3) even in the intermediate and basal cells; this OTC-mediated ACh uptake from the epithelium could be inhibited by trospium. In summary, these results demonstrate a truly novel and exciting insight into an urothelial non-neuronal cholinergic system that differs widely from that found in neurons with respect to the molecular components of the ACh synthesis and release mechanisms. As a consequence, these two systems might be targeted differentially by pharmacological approaches [79, 84].

However, these data also indicate that increased release of basal ACh from neuronal or non-neuronal sources during bladder filling, which directly or indirectly increases the excitability of afferent pathways in the bladder, probably contributes to the symptoms of OAB [8, 51, 59, 135]. Studies in rats showed that activation of muscarinic ACh receptors in the bladder during the storage phase could indeed induce detrusor overactivity mediated by capsaicin-resistant afferent pathways and/or detrusor muscles [92]. If increased ACh release or action is reduced or prevented by muscarinic receptor blockade, then it is conceivable that afferent activity during bladder storage may be reduced as well.

The abovementioned rat bladder experiments demonstrated that intravesical instillation of various antimuscarinic agents (oxybutynin, tropsium chloride, tolterodine, dime-thindene) at clinically relevant concentrations suppressed carbachol-induced bladder overactivity without affecting bladder contraction pressure [75, 76]. As described, human urine excreted after oral administration of trospium and instilled in rat bladders prevented the carbachol-induced reduction of bladder capacity and intercontraction intervals [77]. Recent investigations in a rat model also demonstrated that intravesical oxybutynin decreased the afferent spike rate and afferent sensitivity in both myelinated (Ad) and unmyelinated (C) pelvic nerve fibres during bladder filling [38]. Altogether, the data suggest that antimuscarinic agents should be effective in treating OAB, not only by suppression of muscarinic receptor-mediated detrusor muscle contraction, but also by direct and/or indirect local inhibitory effects on muscarinic receptors in the urothelium and/or other peripheral sensory pathways during the storage phase of the micturition reflex [14, 38, 76, 77, 84, 101].

**Pre-synaptic muscarinic receptors**

Pre-synaptic muscarinic receptors have been identified in the human bladder on cholinergic and adrenergic nerve terminals, where facilitatory M1 receptors [117] and inhibitory M2 and M4 receptors [35] modulate the release of neuronal transmitters (ACh) in the urinary bladder. The functional relevance of these receptors has yet to be fully elucidated.

It is still unclear whether overactivity of the bladder is mainly caused by increased activity of “normal” M3-mediated bladder contraction, an increased contribution of M2 receptors to the contractile response, or an increase in the sensory limb of micturition. Recent findings on muscarinic receptor function and behaviour in the human urinary bladder indicate that all five muscarinic receptors function in neuronal and non-neuronal cholinergic systems. The receptor subtypes M3 and M4 are both absolutely vital for the normal micturition process and both play a relevant role in the pathogenesis of OAB. Therefore, a muscarinic antagonist used for treatment of OAB should ideally have a distinct M3 receptor affinity and
adequate M₃ affinity, thus achieving an optimal balance between drug efficacy and tolerability. Highly selective binding affinity of an antimuscarinic agent to one special muscarinic receptor subtype does not appear to be therapeutically advantageous in the light of current understanding of pathophysiological processes in OAB. However, all antimuscarinic drugs approved for OAB treatment so far have varying affinities for the different muscarinic receptor subtypes (Tab. 2).

A comparative study showed that tolterodine and oxybutynin have relatively higher affinities for M₃ receptors than for M₂ receptors [65, 99].

The same is true of the new antimuscarinics solifenacin and darifenacin. There have been claims that certain drugs, such as darifenacin, are selective for a specific M receptor subtype (M₃), but comparison of pKi values of the drugs solifenacin, darifenacin and oxybutynin for different receptor subtypes easily dispel these claims. Receptor-binding studies also revealed that trospium chloride is a broad-spectrum antimuscarinic agent [147] with approximately equal affinity for all five muscarinic receptor subtypes (M₁-M₅). Trospium achieves a nearly perfect balance in terms of selectivity for M₂ and M₃ receptors, with a ratio of 1.3 [89, 99]. Moreover, the affinity of trospium for M₂ and M₄ is substantially higher than that of all other antimuscarinics used for OAB. Recent radioligand binding studies demonstrated that commonly used muscarinic antagonists bind with high affinity to muscarinic receptors in the detrusor and mucosa [91, 101]. Trospium has a four times higher affinity for mucosal receptors than for detrusor receptors, whilst darifenacin (M₃ selective) appears to have higher affinity for detrusor receptors. Fesoterodine (M₃ preference) and oxybutynin displayed similar affinities for muscarinic receptors in detrusor and mucosal locations [91]. These findings reinforce the assumption that antimuscarinic drugs interact with receptors within the detrusor as well as in the human mucosa [84, 89, 101].

**Emerging influences on CNS functions**

Owing to the pharmacological properties of anticholinergics they affect not only the target organ but also any other organ with cholinergic receptors. Non-bladder activity may result in dose-limiting adverse effects that restrict the usefulness of these drugs. Such effects cannot be excluded when non-organ-selective substances are used. Since all antimuscarinics currently used for treatment of OAB lack selectivity for the bladder, they all have the potential to antagonise muscarinic receptors, even in the brain. As a result, they may impair certain cognitive processes if they are able to cross the blood-brain-barrier (BBB). All five M receptor subtypes are distributed throughout the human brain [54] (Tab. 3). Postsynaptic M₁ and M₄ receptors appear to be primarily involved in cognitive and motor function, whereas central pre-synaptic M₂ receptors appear to be involved in inhibiting ACh release. M₃ receptors, which are predominantly found in the substantia nigra, are probably involved in the release of dopamine [54]. Slow neuronal excitations mediated by M₁, M₃ and M₅ receptors are post-synaptic processes that stimulate cortical and hippocampal activation of M₂ and M₄ receptors through inositol phosphate turnover. Since none of the available antimuscarinics selectively acts on one muscarinic receptor subtype only, the observed CNS adverse effects of

<table>
<thead>
<tr>
<th>Antimuscarinic drug</th>
<th>Muscarinic receptor subtype binding affinity (pKi) (SEM)</th>
<th>Ratio for mean pKi values (antilog of difference)²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M1</td>
<td>M2</td>
</tr>
<tr>
<td>Solifenacin#</td>
<td>7.6 (0.056)</td>
<td>6.9 (0.034)</td>
</tr>
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<td>Darifenacin</td>
<td>8.2 (0.04)</td>
<td>7.4 (0.1)</td>
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<td>Tolterodine</td>
<td>8.8 (0.01)</td>
<td>8.0 (0.1)</td>
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<tr>
<td>Oxybutynin</td>
<td>8.7 (0.04)</td>
<td>7.8 (0.1)</td>
</tr>
<tr>
<td>Propiverine</td>
<td>6.6 (0.1)</td>
<td>5.4 (0.1)</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>9.1 (0.1)</td>
<td>9.2 (0.1)</td>
</tr>
</tbody>
</table>

pKi (affinity constant) data presented as mean (± standard error of the mean (SEM) (n = 3-6); a difference of 1 decimal power between drugs is significant.

*p ratios were compared by ANOVA: *p < 0.05; **p < 0.001; b although statistically significant, unlikely to be biologically relevant; c statistically significant selectivity for M₁ although unlikely to be biologically relevant.

Table 2: Affinity (pKi) of antimuscarinic drugs for the human recombinant receptor subtypes M1-M5 and comparison of M3-selectivity of each substance [#65, 99].
anticholinergics are likely to result from blockade of multiple receptors, including M1.

The cholinergic system is a major neuromodulatory neurotransmitter system that interacts with core regions of the brain and affects learning and memory function. Cholinergic function is severely reduced in patients with cerebral disorders such as Alzheimer’s disease and cognitive impairment. CNS-related effects of anticholinergic medications are of relevance for any age group, and there is growing concern particularly among geriatricians, urologists and neurologists who treat older patients with multiple co-morbidities and cognitive deficits [4, 69, 70, 129]. The high prevalence of anticholinergic effects in the elderly can largely be attributed to high prescription rates of (1) anticholinergic drugs used specifically for treatment of OAB, (2) other drugs with direct anticholinergic effects (e.g. anti-Parkinson’s, mydriatics, bronchodilators), (3) drugs with indirect antimuscarinic action (e.g. antiarrhythmics, antihistamines, antidepressants, antipsychotics, antiulcer drugs) and (4) over-the-counter medications (e.g. ranitidine, cimetidine) with substantial anticholinergic effects [4, 137].

The cumulative effect of these medications in susceptible elderly patients with early-stage dementia, age-associated memory impairment or mild cognitive impairment may precipitate early cognitive declines or further exacerbate cognitive deficits in those already suffering from dementia. Thus, elderly OAB patients often have an increased anticholinergic burden and therefore are at risk of anticholinergic toxicity. The decrease in metabolism and elimination and the increase in drug interactions in the elderly are additional factors resulting in increased anticholinergic loads [7, 137].

Not every drug with anticholinergic activity influences cerebral function to the same degree. This is an important fact to consider when selecting an OAB medication. Drugs that can augment non-specific anticholinergic activity should be avoided, especially in susceptible populations. Since cognitive function is normally not evaluated before treating patients for OAB, it is difficult to determine how many patients develop cognitive impairment due to antimuscarinic therapy. The risk and extent to which a drug affecting the cholinergic system is likely to cause CNS impairment depends on its ability to cross the BBB and on its receptor specificity, that means the extent to which it will block the critical receptors (i.e. M1).

To enter the brain, drugs must cross the BBB, which is composed of a single layer of endothelial cells connected by tight junctions. Brain microvascular endothelial cells lack fenestrations, have few pinocytotic vesicles, and express a variety of metabolic enzymes and membrane efflux transporters [12, 48, 54, 103, 127]. Thus, the BBB is not just a passive anatomical lipid-phase membrane, but is rather a dynamic interface containing both physical and metabolic (transporter) components. Whereas diffusion through paracellular spaces is almost negligible owing to the tight junctions, passive permeation across the endothelial cells is supplemented by a variety of transport proteins in the luminal and abluminal membrane of endothelial cells which actively regulate the transport of nutrients, drugs and metabolites into and out of the brain [12, 41, 48, 127] (Fig. 3).

Assuming that the BBB is intact, the ability of a drug to enter the brain by passive permeation is primarily a function of the drug’s physicochemical properties, namely lipophilicity, molecular charge and molecular size. High lipophilicity, small molecular size and low charge are properties that enhance passive diffusion across cell membranes [41, 103, 132]. Tertiary amines generally have higher lipophilicity and lower mo-

<table>
<thead>
<tr>
<th>Cortex</th>
<th>M1 &gt; M4 &gt; M2 &gt; M3</th>
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<tbody>
<tr>
<td>Hippocampus</td>
<td>M1 &gt; M4 &gt; M2 &gt; M5 &gt; M3 (the only brain region where all subtypes are represented)</td>
</tr>
<tr>
<td>Basal forebrain</td>
<td>M2 &gt; M3</td>
</tr>
<tr>
<td>Thalamus</td>
<td>M2 &gt; M3 &gt; M1 &gt; M4</td>
</tr>
<tr>
<td>Striatum</td>
<td>M4 &gt; M1 &gt; M2 &gt; M3</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>M5</td>
</tr>
<tr>
<td>Brainstem, cranial nerves</td>
<td>M2 &gt; M4</td>
</tr>
</tbody>
</table>

Table 3: Distribution of muscarinic receptor subtypes in the CNS [54].

Fig. 3. Model of drug transport across the blood-brain barrier.
Several physiological studies have already been performed to evaluate whether the various antimuscarinics used for treatment of OAB produce changes in brainwave activity. Quantitative electroencephalography (qEEG) was used as a physiological measure of sedation to evaluate the CNS effects of trospium chloride and oxybutynin in 12 healthy young males (age 26 ± 4 years) [104]. Single 20 mg doses of oxybutynin caused significant decreases in alpha and beta-1 waves, whereas trospium given either orally (45 mg) or intravenously (1.2 mg) did not cause any recognisable changes in brainwave activity. Accordingly, trospium chloride has not been observed to cause adverse CNS reactions in any clinical trial, even with extremely high oral doses of up to 360 mg [24, 95].

Another randomised controlled trial (RCT) compared the effect of acute doses of tolterodine IR 4 mg, trospium 45 mg and oxybutynin 20 mg on daytime EEG parameters in 64 healthy young males (age 25 ± 3 years) [124]. Oxybutynin significantly reduced the power of four different frequency bands (p < 0.01), which is consistent with a probable direct CNS effect; the maximum effect occurred 1–2 h after administration. In contrast, tolterodine and trospium induced only marginal effects, as shown by a slight theta power reduction. The distinct central effects of oxybutynin reflect its high CNS penetration and may be due to direct or indirect interaction with specific transmitter systems. Drug tolerability was comparable between groups, although the frequency of CNS-related adverse events was higher in the oxybutynin group (17 events) than in the trospium (11 events) and tolterodine (5 events) groups [124]. The results for tolterodine and trospium are in agreement with data from another placebo-controlled trial using qEEG and auditory evoked potentials (P300) for assessment of cognitive function [109].

To determine the extent to which antimuscarinic drugs used for OAB depress CNS function, their effects on sleep parameters and cognitive function were additionally investigated. Sleep is not a passive state of unconsciousness, but rather a dynamic brain process, which plays an important role in the restoration of physical and mental functioning [118]. There is strong evidence that anticholinergic compounds influence sleep structure and quality [131]. Suppression of rapid eye movement (REM) sleep appears in the sleep profile as an increase in REM latency (the time between sleep onset and the first period of REM) or as a reduction in REM sleep duration (% of total sleep time). Anticholinergics also influence non-REM and wake periods of sleep, which characterise the degree of sedation. A recent RCT [39] demonstrated that single doses of 15 mg oxybutynin and 4 mg tolterodine (the recommended daily doses) significantly reduced REM sleep duration by approximately 14 %, and 15 %, respectively, and insignificantly prolonged REM latency compared with trospium chloride (45 mg) and placebo in 24 elderly volunteers.
aged 51–65 years. Polysomnography was performed between 10:30 p.m. and after spontaneous awakening or by 6:30 a.m. at the latest. Thus, comparable experimental conditions were used to analyse the different drugs with regard to their individual Cmax. Single doses of the tested antimuscarinics did not affect cognitive skills or other objective and subjective sleep variables in these individuals. This trial verified the results of an earlier study in the main target population for OAB treatment, namely individuals aged ≥ 50 years. In this previous study [40] with the same design (randomised, double-blind, placebo-controlled, crossover), a single 15 mg dose of oxybutynin influenced sleep structure as was reflected by REM suppression and mild sedation, whereas trospium (45 mg) and tolterodine (4 mg) did not. Subjective results from sleep questionnaires and data from psychometric tests were not markedly different. However, the young healthy volunteers (age 22–36 years) recruited in this trial are not the relevant population for OAB treatment. Recent data suggested that tolterodine and oxybutynin cross the BBB in older subjects, whereas trospium does not [39].

These studies investigated the effects of antimuscarinics only after a single albeit therapeutically relevant dose. However, these drugs are normally used to treat patients with chronic diseases, and are generally administered for extended periods of time. Thus, it is still unknown how the acute effects on sleep structure evolve during long-term use. A large phase III RCT performed in the USA provides additional clinical support for the fact that conventional clinical doses of trospium do not increase daytime sleepiness or affect alertness levels, even when used for longer periods of time [119]. In this study the Stanford Sleepiness Scale (SSS, validated) was used to assess the effects on sleepiness in 658 OAB patients. The mean changes in SSS scores (from baseline) at weeks 1, 4 and 12 and at the estimated time of Cmax for trospium were minimal, clinically irrelevant, and comparable with those measured in the placebo group. There was no variation in these findings across age groups.

None of the aforementioned clinical studies reported any effects of anticholinergic therapy on cognitive skills, but different effects on quantitative pharmacological parameters (EEG, REM sleep) have been detected. Impairment of cognitive function by several of these drugs has been observed in clinical trials as well as in medical practice. Two cognitive studies of the OAB drug darifenacin [71, 85] demonstrated an absence of any effect of darifenacin on cognitive function in healthy volunteers, although significant changes in qEEG recordings were observed during the first hours after dosing [71]. The SPC of darifenacin also listed relevant CNS adverse effects. However, there is no correlation between objective physiological findings and performance findings. It therefore seems doubtful whether and to what extent the available cognitive tests are truly clinically useful tools for detecting impairment of CNS function. However, in the light of the described study findings, impairment of cognitive skills and neuropsychological side effects cannot be excluded, especially when elderly patients with impaired REM sleep due to various psychiatric diseases (e.g. depression) and/or sleep disorders are treated with the antimuscarinic drugs oxybutynin and tolterodine.

Summarising these data, it is evident that currently available antimuscarinics penetrate the CNS to a variable extent depending on their physicochemical properties. Trospium appears to have little or no capability of crossing the BBB under normal conditions. It does not have any significant influence on qEEG parameters or any clinically relevant CNS effects. Nevertheless, CNS penetration can be influenced by several factors that can alter the integrity of the BBB. If the BBB is impaired because of these factors, drugs that normally have little or no ability to cross the BBB may now have an increased probability of penetrating the CNS. Nonetheless, drugs with normally restricted entry may still have a definite advantage over those drugs with a high inherent potential to enter the brain. It is extremely important to remember this when prescribing anticholinergic therapy to elderly patients, who have the highest frequency of OAB, or to patients on multiple co-medications and those with chronic conditions involving the CNS.

CONCLUSIONS

Taken together, the findings highlighted in this review permit only one answer to our question formulated in the title: “No”, antimuscarinic drugs for the treatment of OAB are not all the same! Although their clinical efficacy appears to be largely similar, differences in the physicochemical properties of these drugs and thus in their pharmacodynamic and pharmacokinetic profiles result in important differences in the specific side-effect profile of the individual drugs. When prescribing OAB treatment, the physician should always attempt to minimise the use of medications that can increase non-specific anticholinergic activity, especially in susceptible patients like the elderly. Awareness of the subtle differences between the different available antimuscarinics can help the physician to determine which drug will be the most effective and best tolerated agent and to choose the one that is most appropriate for his patient.

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