The cognitive effect of anticholinergics for patients with overactive bladder

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*Dr Welk & Dr Richardson are co-first authors and contributed equally to this role.

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Abstract

Overactive bladder (OAB) is often treated with medications that block the cholinergic receptors in the bladder (anticholinergics). The effect of this medication class on cognition and risk of dementia has been increasingly studied over the last forty after initial studies suggested that the anticholinergic medication class could affect memory. Additional short-term randomized clinical trials demonstrated that the administration of the anticholinergic oxybutynin leads to impaired memory and attention, and large, population-based studies showed associations between several different anticholinergic medications and dementia. However, trials involving anticholinergics other than oxybutynin have not shown such substantial effects on short-term cognitive function. This discordance in results between short-term cognitive safety and long-term increased dementia risk could be explained by the high proportion of patients using oxybutynin in the dementia studies, or a study duration that was too short in the prospective clinical trials on cognition with other anticholinergics. Notably, all studies must be interpreted in the context of potential confounding factors, such as when prodromal urinary symptoms associated with worsening dementia lead to an increase in OAB medication use, rather than the increase in medication use causing worsening dementia. When necessary in patients with potential risk factors for cognitive impairment, the cautious use of selected OAB anticholinergic agents with favourable physicochemical and pharmacokinetic properties and clinical trial evidence of cognitive safety might be appropriate.

Introduction

Overactive bladder (OAB) is a common condition that affects ~10–15% of the population, has increased frequency as people age, is found more frequent in women, and has substantial direct and indirect costs accounting for billions of dollars of worldwide health care expenditure.[1] OAB

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is defined by the International Continence Society as urgency, with or without urge incontinence, usually with frequency and nocturia.[2] OAB is a chronic condition, with only a small proportion of patients experiencing spontaneous remission of their symptoms.[3] The understanding of the aetiology of OAB has progressed in the past few decades, and several potential OAB phenotypes and pathological mechanisms have been identified.[4] The myogenic mechanism (which links detrusor overactivity to OAB) is perhaps the most well-known, however only half of women with OAB have detrusor overactivity on urodynamics.

The management of OAB has been well described in societal guides, such as those from the AUA[5] and the EAU[6]. In general, guidelines recommend initial conservative interventions and lifestyle modification strategies (such as fluid modification, timed voiding, and pelvic floor exercises), and then a trial of medical therapy for patients with bothersome symptoms. The first drug therapies for OAB were anticholinergic medications which the FDA approved in 1970 (flavoxate), and 1975 (oxybutynin).[7] Over time, several additional medications (such as tolterodine, trospium, darifenacin, solifenacin, and fesoterodine) with various pharmacodynamic properties (still considered part of the anticholinergic class) were developed and approved for use in patients with OAB. [8] These medications block cholinergic receptors in the bladder which reduces spontaneous myocyte activity.[8] All these medications have demonstrated similar efficacy, with meta-analyses suggesting an average reduction of 0.5–1.0 episodes of incontinence per day, 0.5–1.3 fewer micturition's per day and 0.6 –1.5 fewer episodes of urgency per day[9,10]; in a high quality randomized study of 249 women, the cure rate for urge urinary incontinence (OAB with incontinence) in the cohort treated with solifenacin was 13%.[11] However, long-term adherence to therapy is modest, with only 10–40% continuing with medical therapy after a year.[12] This limited persistence is, in part, caused by the adverse effects associated with anticholinergic medications, which include gastrointestinal, ocular, urinary tract, neurological, and cardiovascular effects.[13] Many specific adverse effects (such as dry mouth and constipation) are well recognized, but large, population-based observational studies have demonstrated that exposure to anticholinergic medications might also increase the risk of dementia[14,15], and exposure to only a few weeks of oxybutynin in a study of 150 healthy individuals was associated with measurable cognitive impairment.[16] These neurological effects are particularly relevant, as

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they can result in considerable loss of independence, are associated with morbidity, and have substantial societal and health care costs.[17,18] From a patient perspective, cognitive impairment is the most unwanted anticholinergic adverse effect.[19]

Guidelines[5,6] do mention cognitive impairment as a potential consideration when prescribing anticholinergic medication, although only the American Urogynecology Society has specifically addressed this topic in relation to OAB.[20] Their recommendations are to counsel patients about the risks of cognitive side effects when using OAB anticholinergics, minimise the total anticholinergic burden for the patient, and consider non-anticholinergic therapies for OAB if patients are concerned about cognitive side-effects. Challenges exist in addressing the relationship between cognitive impairment and OAB anticholinergics: small randomized trials examining short-term cognitive function suggest several of the more contemporary OAB anticholinergics are safe[16,21–27], many of the large, observational studies showing an increased risk of dementia with anticholinergics are not exclusively studying OAB anticholinergics[14,15] and these studies could have been susceptible to protopathic bias. Lower urinary tract (LUT) symptoms (including urinary urgency, the hallmark of OAB) are a prodromal syndrome of cognitive impairment and dementia, and often predate the appearance of neurological symptoms [28]. This prodromal syndrome can lead to a biased risk assessment in observational studies, as patients taking anticholinergic medications for their LUT symptoms might have already been in the early stages of neurological decline.

Physicians who treat OAB need to understand the potential cognitive hazards associated with anticholinergic therapy and be able to weigh the risks and benefits associated with the long-term use of these medications. In this Review we summarize the mechanisms by which OAB anticholinergics might effect cognition and/or dementia risk, and review and critique the clinical evidence specifically related to OAB anticholinergics.

CNS effects of anticholinergics

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All the muscarinic receptor subtypes have been identified in the CNS. Animal and clinical studies from the 1980's have identified the potential negative effect of anticholinergics on the brain.[29]

Distribution of cholinergic receptors

In the central nervous system (CNS), acetylcholine-producing neurons in the cholinergic basal forebrain project to the neocortex, amygdala, and hippocampal formation, and the brainstem cholinergic neurons project to the midbrain and hindbrain.[30] The cholinergic neural circuitry has several vital roles ranging from high-level functions such as learning, memory, attention, sensorimotor processing, to low-level functions such as sleep–wake cycles and arousal.[31–33] The five subtypes (M1-M5) of muscarinic acetylcholine receptors (mAchRs) are expressed in different brain regions;[33,34] the M1 receptor is highly expressed (followed by M2 and M4 subtypes) in the hippocampus[35] and the frontal, temporal, parietal, and occipital neocortices[36] (Figure 1). The density of mAChR expression is highest in the striatum and M1 and M4 are the most abundant subtypes. By contrast, in the LUT, the most widely distributed mAChR is the M3 subtype, although the M2 receptor is functionally most relevant.[8]

Mechanism of cognitive decline

Clinical studies suggest that the ability of certain anticholinergic medications to exert CNS effects is through antagonism of the M1 subtype of mAChR, and to an extent M2 and M4 receptors, resulting in diminished central cholinergic activity. Reduction of cholinergic functions and reserve predisposes to impaired cognitive performance, and in susceptible individuals, memory impairment.[38–40]

It is likely that there are factors that increase the susceptibility to developing central anticholinergic side effects though this remains unclear. APOE-ε4 allele is a genetic risk factor for Alzheimer's disease found in about 14% of the population and a preliminary study of 24 patients suggested that carriers of this allele (a) have an increased risk of anticholinergic treatment-induced memory deficits compared to non- APOE-ε4 participants.[41] The allele affects Aβ aggregation and clearance thereby playing a major role in Alzheimer's pathogenesis, however has also been shown to be associated with impaired cholinergic sprouting in *APOE4-*

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transgenic mice post-injury (DOI: 10.1016/j.nbd.2005.08.010). In a study of 688 cognitively normal people, the presence of protein biomarkers associated with Alzheimer's disease tau and abeta in cerebrospinal fluid and exposure to anticholinergic medications significantly increased the risk of future mild cognitive impairment (HR 4.25, p<0.01), compared to patients with only anticholinergic medication exposure (HR 1.42, p=0.02).[42] In a small single-blind observational study, central adverse effects such as decline in the mini-mental state examination (MMSE) and behavioural changes occurring with short-duration use of anticholinergic bladder medications reversed on cessation of the drug[43] suggesting that the length of exposure to medications may influence reversibility following cessation.

Anticholinergic burden

The concomitant use of different agents with anticholinergic properties is also likely to predispose to developing cognitive dysfunction. There are many medications that have anticholinergic effects, and they are used to treat conditions such as diarrhea, nausea, symptoms of neurologic diseases (such as Parkinson's disease), dizziness, allergies, depression, psychosis, and skeletal muscle spasm.[58] Potential side effects of anticholinergic medications include delirium, tachycardia, dry eyes and dilated pupils, constipation, dry mouth, and decreased sweating.[58] Cumulative anticholinergic exposure, called the anticholinergic burden, has been linked to a number of adverse outcomes such as cognitive impairment, increased risk of falls, hospitalization and death.[59,60] To date, 19 different anticholinergic burden scales have been designed that quantify the cumulative exposure to anticholinergic activity.[61] However, no gold-standard assessment exists to determine how 'strong' an anticholinergic effect a medication has, or how to best assess the total anticholinergic burden a patient might be exposed to. Considerable heterogeneity exists between scales owing to the use of different methods of anticholinergic burden assessment (expert opinion, clinical anticholinergic effects or in vitro testing), use of different scoring systems and application in different clinical settings.[62] For example, one review of anticholinergic burden scales in 5,323 patients with dementia found the prevalence of anticholinergic exposure varied between 36–69% depending upon which scale was used.[63]

The association between adverse outcomes and anticholinergic burden varies between scores and has not been conclusively established; however, across all scales bladder anticholinergic agents

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are consistently considered strong anticholinergics that make a large contribution to the overall anticholinergic burden.[62]

Pathological and radiological evidence

Brain histopathological and neuroimaging studies have demonstrated associations between anticholinergic medication exposure and structural and functional changes. In a study of community-dwelling older adults (mean age 52), exposure to anticholinergic medications without known clinical relevant cognitive effects was associated with greater rates of atrophy in total cortical grey matter volume compared to people who did not use anticholinergics (relative difference -1.13 cm^3/year of total grey matter, p=0.01).[64] In the cognitively normal older person, use of anticholinergic medications is associated with increased brain atrophy, particularly in the temporal lobe (which plays a role in language and memory).[65] Results of autopsy studies exploring Alzheimer-type pathology (amyloid plaques and neurofibrillary tangles) in the brain tissue of patients treated with anticholinergic medications are conflicting. In one study there was a significant 2.5-fold increase (p<0.01) in plaques and tangles in the brains of patients with Parkinson's disease using anticholinergics for >2 years (n=18) compared to the brains of patients with Parkinson's disease not receiving anticholinergics (n=21).[66] However, no evidence of an increase in typical Alzheimer's disease pathology was observed in studies evaluating brains from 51 patients without Parkinson's disease compared with patients not treated with anticholinergics (OR 0.40 (95% CI 0.18–0.87), or among 420 people who had autopsy results available from a prospective dementia-free cohort of adults >65 years of age.[67,68]

A functional MRI imaging study in healthy older adults (n=34) without OAB (mean age 74 years, standard deviation 6.7) demonstrated that scopolamine (a medication with strong anticholinergic effects) reduced baseline scores on the Buschke Selective Reminding Task (a measure of verbal learning and memory) and this reduction in task score correlated with reduced MRI measures of neural connectivity in different cortical networks.[69] A randomized trial of hypnosis versus anticholinergic medications in patients with OAB (n=64) showed that both hypnosis and anticholinergic therapy resulted in improved OAB symptoms on 3-day voiding

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diaries, and increased the functional connectivity (measured by predefined regions of interest from the functional MRI images) of the dorsal attentional network.[70]

Anticholinergic pharmacodynamic properties

For anticholinergic medications to influence cognition, they must be able to directly interact with the CNS. This interaction however is influenced by their pharmacodynamic properties that determine their ability to cross the blood–brain barrier (BBB) and the distribution of mAChR subtypes in the CNS.

The penetration of drugs into the CNS is determined by the permeability of the BBB, which is governed by specialized endothelial cells of the capillary walls supported by a basal membrane, pericytes and astrocytic end-feet.[44] The presence of tight (zonulae occludens) and adherens between cells physically blocks paracellular transport, and the BBB regulates the transport of molecules between the vascular spaces and brain parenchyma.[45] Drugs that freely cross the BBB would be expected to attain high concentrations within the brain[46]; however, physicochemical properties of these molecules (such as their polar surface area, molecular weight, lipophilicity and hydrogen bond donors) impart selective permeability across the BBB (figure 2).[47] Amongst anticholinergic agents used for OAB, those agents with increased molecular weight such as darifenacin and 5-hydroxymethyl tolterodine (5-HMT, the active metabolite of fesoterodine), or those having hydrophilic properties owing to the presence of a quaternary amine group that is ionized at physiological pH (such as trospium) are expected to have reduced ability to cross the intact BBB (due to unfavorable physicochemical interactions).[46,48] Efflux transporter proteins **[G]** on the BBB can also influence drug entry into the CNS; the best studied of these proteins is P-glycoprotein (P-gp), which is present on the basolateral membrane of capillary endothelial cells.[49] Substrates with an affinity for the P-gp efflux transporter, such as 5-HMT, darifenacin and trospium, are, therefore, actively expelled from the CNS.[46,50] Notably, certain medications, such as statins and proton-pump inhibitors can decrease the activity of the P-gp efflux transporter, and various genetic variations in the structure of the P-gp protein can also affect its function.[51]

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The results of in vivo experiments in rats have shown CNS penetration to be the greatest for oxybutynin, and the least for trospium, darifenacin and 5-HMT.[46] Moreover, although drugs such as 5-HMT are associated with considerable central anticholinergic activity in brain tissue in vitro, others such as darifenacin have low binding affinity.[52] This variation in CNS activity is attributable to the greater affinity of some anticholinergic agents (such as darifenacin) for the M2 and/or 3 receptors than the M1 receptor, which could have more selective effects on the LUT, sparing the CNS.[46] Most other OAB anticholinergics are non-selective (for example, oxybutynin, tolterodine, fesoterodine), or only weakly selective (for example, solifenacin) for the bladder related mAChRs.[46,53] In a rat model, positron emission tomography demonstrated that mAChR antagonism in the CNS was highest with oxybutynin, and lowest with darifenacin.[54]

The implications of these observations for humans is uncertain. Increasing age, use of certain medications and the presence of illnesses such as diabetes, neurological disease and stress can influence passive permeability and active transport mechanisms across the BBB.[55,56] Thus, in human, particularly those with relevant co-morbidities, (which includes the vast majority of patients with OAB[57]) all anticholinergic agents should be considered to have the potential to cross the BBB.

Cognitive effects of anticholinergics

Cognitive changes have been a long-recognised acute complication associated with anticholinergic medications. However, OAB anticholinergics have generally been well-tolerated in short term *clinical* studies, and there is limited data to suggest that OAB anticholinergics lead to an increased risk of dementia.

Short-term cognitive effects

Concerns raised by researchers about cognitive changes resulting from administration of this class of medications have led to several randomized clinical studies assessing the effect of OAB medications on cognition (Table 1), with 9 out of 12 of the trials sponsored by pharmaceutical companies, reflecting the uncertainty over cognitive safety.[16,21–27,71–74] Most of these studies used a variety validated neuropsychology tests that evaluate different cognitive areas including

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memory, attention, and executive functioning and were administered in a controlled and standardized setting after use of specific medications of interest. The duration of OAB anticholinergic therapy in these studies varied from a single dose to 8 weeks of regular therapy.

In one of the earliest randomized trials with a cognitive outcome, oxybutynin was compared with diphenhydramine (an anticholinergic medication for nausea) and placebo [71] in healthy people with a mean age of 69 (n=12).[71] Decreased memory and reaction times were demonstrated compared with placebo 90 minutes after a single dose of oxybutynin (no change, compared with placebo, was found with diphenhydramine). Notably, oxybutynin has been used as an active comparator (or positive control) in studies of other OAB medications because of its hypothesized substantial effect on cognition.[16,21,24,72] Compared with placebo, oxybutynin decreased scores on various outcomes such as memory tests[16,24] and measures of attention[21,24] and also impaired electroencephalogram (EEG) readings[72] and rapid-eye movement sleep (which is a surrogate marker for cognitive effects).[75] However, in a small population of older women resident in nursing homes (n=50, mean age 89) with cognitive impairment,[73] no difference in cognitive function was found with 4 week oxybutynin treatment compared with placebo, although this outcome could have occurred because very low dosages of oxybutynin were used (5mg extended release), or because the chosen outcome measures were not sensitive enough to detect change in patients with severe baseline impairment. In another study of 153 health people (mean age 68), neither oxybutynin 10% topical gel, placebo or the active control, oral oxybutynin 15mg intermediate release, significantly reduced scores on the name-face association test (p=0.27)[74] (although oxybutynin did impair immediate and delayed recall, and lead to a lower score on the misplaced objects test).

Short-term cognitive effects of other anticholinergics have also been assessed in randomized trials. The effect of tolterodine on neural activity was assessed using EEG[72] in a randomized trial of 64 healthy young men (aged 18–35) without OAB. An EEG was performed after a single dose of oxybutynin, tolterodine, trospium, or placebo, and outcomes demonstrated that a single dose of oxybutynin significantly reduced (p<0.01) the power in several EEG frequency bands **[G]**, whereas tolterodine and trospium had only a small significant effect (p<0.05) on one frequency band (theta).

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Three randomized trials evaluating the M3 receptor selective drug darifenacin demonstrated that a range of different doses and formulations did not substantially effect different cognitive tests after 1–3 weeks of use in either healthy older people without OAB (n=150, age 60-83)[16], 27 healthy men (age 19-44 years)[23], or 129 health volunteers (mean age 71, range 65-84)[22] when compared with placebo.[16,22,23]

Consistent with the hypothesis that trospium should not be able to cross the BBB, a study in 45 healthy women showed no significant change (p=0.29) in cognitive function after 4 weeks of treatment with 60mg of the extended release formulation compared with placebo,[26] and even in combination with high doses (20mg) of solifenacin, no measured cognitive impairment was demonstrated[27]. Trospium was not detected in the cerebrospinal fluid of 12 healthy older (aged 65–75 years) volunteers without OAB,[76] and the use of trospium in 212 patients with dementia and urge incontinence did not lead to a significant decline in cognitive scores after 6 months (p>0.05).[77]

A placebo-controlled, randomised trial of a single dose of solifenacin (which is weakly M3 selective) did not significantly affect measures of cognition among a small group of 12 healthy older (aged 65–75 years) patients (p>0.05)[24]. In a randomized trial of 26 healthy older patients (mean age of 80 years) with mild cognitive impairment treated for 3 weeks with solifenacin 5mg, no significant change was found in cognitive outcomes compared to placebo (p=0.38-0.63) .[21] In a placebo-controlled, randomised trial of 18 healthy volunteers >65 years of age, fesoterodine in both the 4mg and 8mg dose also did not significantly effect the chosen cognitive outcomes after 1 week of therapy compared with placebo (p>0.05).[25]

Limitations in all of these randomized studies include that the patient populations were usually restricted to healthy, older cognitively intact patients without OAB (although clinical trials of oxybutynin[73] and solifenacin[21] were carried out in cognitively compromised populations). Additionally, outcome measures used in these studies were quite variable, and difficult to compare across studies. Treatment periods were generally short, with 11 out of 12 of the

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randomized trials exposing patients to 4 weeks or less of OAB medication, and only half of the clinical trials[16,21,23,25,72,74] included an active comparator to ensure that the outcome measures and sample size were appropriate to detect cognitive changes. Determining the clinical relevance of some of the deleterious cognitive changes that were observed with oxybutynin is difficult as the changes in cognitive test scores often do not have a clinically relevant anchor; however one study related the cognitive score-change with anticholinergics to the cognitive changes associated with normative ageing, and found oxybutynin's negative effect after 3 weeks was equivalent to 10 years of cognitive ageing[16].

Long-term cognitive decline

In total, three clinical studies have examined OAB anticholinergics and cognitive decline over a 6–12 month period (Table 2). A prospective **cohort** study followed 164 women with or without OAB (mean age 77).[78] An unadjusted mean 0.37 point greater impairment in the Montreal Cognitive Assessment (MOCA) score (p=0.53) was observed over 12 months in the OAB patients taking oxybutynin or trospium, compared with the non-OAB group. However, the proportion of women completing the study was low (with ~40% drop out in each of the groups), therefore, cognitive decline in the anticholinergic users might have been underestimated as those patients dropping out recorded lower baseline cognition scores than patients who continued treatment.

A study of 50 outpatients with OAB at a geriatric clinic in Turkey prescribed darifenacin for 6 months had an unadjusted 0.4 point greater decline in mini-mental state examination [G] (MMSE) (*P*=0.04) than in 28 patients who were prescribed pelvic floor exercises and lifestyle modifications.[79] However 12% had dementia at baseline (making interpretation of the results more challenging as patients were not stratified on this variable), and again a large proportion of patients discontinued therapy during the 6 months.

In a retrospective analysis of data from the US National Alzheimer's Co-ordinating Center (NACC) cohort (consisting of people with and without Alzheimer's stratified by bladder anticholinergic use (n=698) and no bladder anticholinergic use (n=7027)), an adjusted odds ratio

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(OR) of 1.40 (95% CI 1.19-1.65) was estimated for any decline in MMSE scores over 12 months, and an OR of 1.21 (95% CI 1.03-1.42) for worsening clinical dementia rating.[80] When stratified by baseline cognition, the normal cognition group did not have a significant increase in MMSE decline (OR 1.26, 95% CI 0.99-1.62). Whens sratified by type of anticholinergic, the users of non-M3 specific bladder anticholinergics did have an increased risk for any decline in MMSE (OR 1.42, 95% CI 1.05–1.92). Analyses of crude MMSE change scores were not presented, but summary statistics suggest the mean decline in MMSE was negligible (0.04 points).

Overall, these clinical studies do not support a clinically relevant decline in cognition over 6–12 months of new OAB anticholinergic use in older adults with normal cognition and without neurological disease. However, the study estimates are probably biased owing to poor long-term monitoring and treatment adherence. Furthermore, the MMSE score is not well-suited to identify mild cognitive impairment.[81] By contrast, observational studies examining all medications with anticholinergic properties find greater long-term decline in global cognitive measures in older people taking strong anticholinergics compared to non-users.[82] However, many of these observational studies also suffer from residual confounding factors as some medications could be prescribed for early symptoms of dementia.

Anticholinergics and dementia risk

Dementia is a significant disease that impairs cognition, and can lead to falls, malnutrition, depression, and institutionalisation. Anticholinergic medication use is one of the potentially modifiable risk factors for dementia.

General anticholinergic medications

Approximately 10% of the older population **(>65 years of age)** are regularly taking medications with strong anticholinergic activity.[83–85] The most common of these medications are tricyclic antidepressants (TCAs), although antipsychotics, antihistamines, and medications for Parkinson's disease and OAB are also prevalent. Many observational studies (using routine electronic records to identify patients with dementia) report associations between the use of

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medications with strong anticholinergic activity and increased incidence of dementia; however, study findings are heterogeneous and probably biased.[82] In 2020, a meta-analysis of seven studies evaluating dementia risk, the estimated pooled OR was 1.20 (95%% CI 1.09–1.32) for any strong anticholinergic use and incident dementia.[82] However, there was substantial heterogeneity among these studies (I^2=86%) primarily from studies with followup of more than one year.

The association between anticholinergic medication use and dementia risk is strongly confounded. Most of the commonly used strong anticholinergic medications are prescribed for conditions that are risk factors for or early symptoms of dementia, such as depression, psychosis, and Parkinson's disease.[15,85] Dementia has an insidious onset, and (based on data from UK primary care) patients have an average of 3 years between recognizing and/or reporting symptoms and then being formally clinically diagnosed.[86] Consequently, a common methodological approach to handling latency periods is to apply a lag-time to study follow-up periods and to exclude any new dementia diagnoses in the first few years following the medication exposure.[15]

In the 2020 meta-analysis, most studies examining general anticholinergic use and incident dementia or long-term cognitive decline were found to have a serious or critical risk of bias.[82] Few studies accounted for confounding by the indications for anticholinergic medication use and rarely were they able to account for confounding by underlying frailty. Many studies did not apply a lag time and, therefore, could be capturing patients who would have been diagnosed with dementia regardless of anticholinergic use. However, the studies that did apply lag times and were able to account for a wide range of confounders (although still at risk of residual confounding) did still report associations with strong anticholinergic use and increased incidence of dementia.[14,15,87,88]

Consistent with a causal link, many studies also reported a greater association of dementia incidence with longer exposure to anticholinergic medications than in patients exposed to shorter durations. Pooled OR from the meta-analysis was estimated at 1.23 (95% CI 1.17–1.29) for

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incident dementia for ≥90 days use and 1.50 (95% CI 1.22–1.85) for ≥365 days use (albeit with substantial heterogeneity for ≥365 days use).[82]

The cognitive effect of anticholinergic medications was initially believed to be cumulative and additive, such that anticholinergic burden scores improve quantification of the overall risk of multiple simultaneous medications.[61] However, little evidence supports the hypothesis that the cumulative use of drugs considered to have a low anticholinergic burden on these scales contributes towards any additional dementia risk.[15,89] The inclusion of this group of anticholinergics medications in the burden scales is the result of expert opinion and not pharmacologic evidence.[90,91] For example, an *in vitro* study of the anticholinergic activity of common medications at clinically relevant doses did not identify central anticholinergic action with coumadin or Lasix, both of which are included in the lower scoring tier of most anticholinergic burden scales.[91] [90,91]However, all OAB anticholinergic medications are generally considered strong anticholinergics in the burden scores.[61]

Despite many studies showing associations with dementia, and evidence of dose-response effects, large observational studies have suggested inconsistencies in associations across drug classes, therefore, contradicting a causal link.[14,15,92] No association was reported between strongly anticholinergic gastrointestinal drugs or antihistamines and incident dementia in any of these studies, which suggests either differential effects across different types of anticholinergic drugs or residual confounding in studies with some of the other anticholinergic drugs (such as antidepressants, antipsychotics and Parkinson's Disease drugs) owing to their use for early symptoms of dementia.

Few studies have examined anticholinergics and dementia risk in specific patient groups. For depression, in one retrospective cohort study, no difference was found dementia incidence between US care home residents with depression who were using paroxetine (n=1,898, which has strong anticholinergic activity), compared with 18,054 residents who were using other selective serotonin reuptake inhibitors **[G]** (SSRIs) with little anticholinergic activity.[93] Results of a US cohort study of 3,059 community-dwelling people over 65 years of age taking antidepressants also showed no association with SSRIs or strongly anticholinergic TCAs and

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dementia, although the findings did show associations between paroxetine prescription and dementia.[94] Results of a cohort study of family practices in the Netherlands (n=3526) showed that the significant association between anticholinergic medication use and dementia (HR 1.95, 95% CI 1.13-3.38) was nonsignificant (HR 0.42, 95% CI 0.06-3.01) when excluding antidepressants and antipsychotics, which suggests there was confounding by indication.[95] In a cohort study in Taiwan of anticholinergics in Parkinson's Disease, ≥6 months exposure to Parkinson's Disease anticholinergics was associated with a hazard ratio (HR) of 1.23 (95% CI 1.10–1.37) for incident dementia after a 1 year lag period.[96] The researchers also demonstrated associations with dementia incidence for concomitant strong anticholinergic use from other classes. However, residual confounding was probably present in this study, as the researchers adjusted for only a small number of covariates. These studies suggest that the relationship between anticholinergic use and dementia is not consistent in all disease states, and anticholinergics with different indications may lead to different associations with dementia risk.

OAB anticholinergic medications

To date, few studies have solely examined OAB anticholinergic use and dementia risk.[97–100] Some large studies examining anticholinergic medications in general have performed sub-group analyses of OAB anticholinergics[14,15,92] (Table 3). Notably, these studies did not capture whether patients actually took the anticholinergic medications, but instead relied upon prescription refill or claims records.

Using data from separate primary care practices in the UK, two large nested case-control studies were performed examining incident dementia: the first used patients from the UK (40,770 with dementia, and 283,933 without dementia, average age 82)[15], and the second also used UK patients from a different primary care database (58,769 with dementia (average age of diagnosis 82), and 225,574 without dementia).[14] Both studies reported sub-group analyses by drug class and cumulative dose. Associations with increased incidence of dementia were observed with a higher stratums of cumulative dose of OAB anticholinergics (predominately oxybutynin and tolterodine), specifically with ORs ≥1.20 once a standard dose of OAB anticholinergic was used for > 90 days. Some associations reported in the smaller study[15] were weaker than the larger

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study[14], owing to the application of a longer lag-period in the smaller study; because medication exposure 4–20 years before dementia diagnosis was examined (rather than 1–11 years before dementia diagnosis for the larger study) and owing to adjustment of confounders at 4 years before dementia diagnosis in the smaller study, rather than at some time before the medication exposure. In the larger study, sensitivity analyses was also performed, showing similar associations between OAB anticholinergic prescription and dementia for men and women.[14] Observed associations were slightly greater for vascular dementia than Alzheimer's Disease, (for the highest standardised daily dose of anticholinergic, the adjusted OR was 1.68 (95% CI, 1.57-1.79) for vascular dementia, and 1.37 (95% CI, 1.30-1.44) for Alzheimer disease). Associations were also slightly greater for dementia diagnosed before the age of 80 years compared to patients less than 80 years of age. Associations were only marginally reduced when restricted to OAB medication exposure occurring 5–20 years prior to dementia.

The findings from the subgroup analyses of these two studies[14,15] should be interpreted with caution, as they probably suffer from residual confounding as the comparator group comprised the general older population not using OAB anticholinergic medications (who, therefore, are unlikely to have potentially prodromal dementia-related bladder symptoms). Elucidating the timing of cause and effect and the timing of confounding effects in case-control studies is difficult.[101,102] However, these nested case-control studies adjusted for a wide range of confounders, and both findings are consistent with each other, suggesting that long-term exposure to OAB anticholinergics is either a risk factor for dementia or a marker of specific patients already being at increased dementia risk.

Various cohort studies have also been published using the Taiwan National Health Insurance Research Dataset (NHIRD).[92,97,98] Patients in these studies were generally followed from an earlier age (average 62–66 years) than the UK studies (average 71–76 years)[14,15]. In a subgroup analysis of 154 patients, a HR for incident dementia of 1.13 (95% CI 0.93–1.23) was reported for any OAB anticholinergic prescription compared with none over the 15 year followup period.[92] Cumulative exposure was further explored in a cohort study (n=16,412) and association with greater dementia incidence was only observed among the two higher cumulative defined daily dose groups compared to the two lower cumulative defined daily dose groups with

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more than 12 months of OAB anticholinergic prescriptions (HR of 1.40 (95% CI 1.12–1.75)).[97] Results of a further matched cohort study from the same Taiwanese database, but specifically evaluating patients with diabetes[98] (with 10,938 OAB anticholinergic users, and 564,733 non-users) showed a greater than two-fold increased risk of dementia in the cohort exposed to oxybutynin, solifenacin, or tolterodine compared with no prescriptions for OAB medication. However, probable residual confounding occurred in this study, as the comparator patients were not matched on either their diabetes severity or their OAB status. In addition, a short lag time (of only 6 months) might have led to over-estimated HRs. These studies were able to adjust for a wide range of health-related confounders, although residual confounding is still possible owing to no information on smoking history and BMI. Notably, considerable overlap was probably present in the patients contributing to each of the three Taiwan studies, as patient data were extracted from the same database.[92,97,98]

In 2020, results of a retrospective cohort study examining US Medicare data showed no difference between M3-selective (darifenacin or solifenacin) and non-selective OAB medications and risk of dementia.[99] Darifenacin is highly selective for the M3 receptor, but the findings in this study could have been influenced by solifenacin, which shows much lower selectivity.[53] The researchers also reported a small increased risk of dementia with > 2 years of exposure to any OAB anticholinergic compared with less than a year of use (ORs 1.11, 95% CI 1.05–1.17 and 1.10, 95% CI 1.04–1.15 for ≥2 and ≥3 years use, respectively), but unfortunately they did not compare with any shorter exposure lengths. The study was methodologically limited by not accounting for mortality or censoring, being unable to determine the timing of the first OAB prescription and having variation in both the lag-times between exposure and dementia diagnosis and timing of covariate measurement relative to the first OAB prescription.

Finally, results of a retrospective cohort study using Canadian linked administrative data (n=70,986) demonstrated a modest HR of 1.23 (95% CI 1.12–1.35) for new OAB anticholinergic prescriptions and risk of dementia compared with first mirabegron (an oral beta-3 agonist used in treatment of OAB) prescriptions in patients over 65 years of age without depression.[100] When stratified by sex, the association was greater in men (HR 1.41, 95% CI 1.23–1.62) and null in women (HR 1.08, 95% CI 0.95–1.23); this may be due to known differences in risk factors for

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progression to dementia between men and women, or the differential effects that anticholinergics have on visual memory and executive function. One of the unique strengths of this study was the use of a matched comparison population which also had OAB and symptoms sufficient to seek out medical therapy, which is important as OAB symptoms can be an early sign of undiagnosed cognitive diseases. This means the groups were more comparable than other studies that used non-OAB patients, or medicated OAB patients as comparators. However, although matched on a wide range of confounders, the effects observed in this study might be overestimated owing to lack of a lag-period, and alternatively underestimated if clinicians were preferentially prescribing mirabegron to patients with cognitive impairment.

The data in context

When considering the literature on cognition and anticholinergic medications, differentiating between cognitive impairment and dementia is important. Dementia is a syndrome of a chronic nature, characterized by a deterioration in memory and other cognitive functions or emotional control that is sufficiently severe to cause social and occupational impairment.[103] Conversely, cognitive impairment refers to objective cognitive decline beyond that expected for age and educational status that is not substantial enough to interfere with daily living.[103] The proportion of patients who progress from cognitive impairment to dementia varies, with a range of 0.3–30%; however, the important distinction is that cognitive impairment can be reversible whereas dementia is not.[103] In older people, early cognitive changes and dementia probably exist on a spectrum of cognitive dysfunction, with the initial development, and then the rate of progression being affected by numerous variables. Cognitive impairment is an insidious process; inhibition of cholinergic activity in neural networks involved in memory and attention has a key role in the development of these early cognitive changes.[30] However, the precise mechanisms underpinning these changes are currently unclear. Dementia is a well-characterised and defined disease condition with specific irreversible pathological changes.[103]

Short-term clinical studies have not shown substantial cognitive impairment with OAB anticholinergics other than oxybutynin (Table 1). Long-term clinical studies on OAB anticholinergics are lacking and those studies that are available are limited by methodological

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issues (Table 2). Cognitive impairment can be reversible or the patient might be able to compensate for changes after a short period of impairment, which explains some of the differences between the short-term and long-term study results. By contrast, a growing number of observational studies suggest a direct association between exposure to anticholinergic agents used for OAB symptoms and future dementia diagnosis (Table 3). Long-term OAB anticholinergic use (in particular use for ≥90 days) is associated with an approximately 20% increased relative risk of dementia[14,15,100], but residual confounding and reverse-causality (in which these medications are being prescribed for early symptoms or prodromes of dementia) cannot be ruled out. Additionally, these studies have largely been carried out using administrative data, which usually does not have detailed cognitive information at baseline, or the ability to identify dementia with 100% sensitivity and specificity.

The apparently discordant results between the prospective short-term clinical studies evaluating the cognitive effect of newer anticholinergics, and the large observational studies evaluating dementia might be as a result of the high proportion of oxybutynin users in the OAB medication subgroups of the observational studies evaluating dementia risk. Short-term use of the novel OAB anticholinergics in the clinical trials (most of which were 4 weeks or less in duration) possibly would not have been sufficient to lead to cognitive changes. The types of patients who receive anticholinergics in the real-world setting (and are the basis for the administrative data studies) may be different from those patients in the prospective clinical trials on cognition.[104] Additionally, many of the randomized clinical trials excluded the co-administration of other anticholinergic medications, which in the real-world setting could potentiate the effects of OAB anticholinergics on cognition.[14] Finally, OAB anticholinergic use could have a lower propensity to cause short-term cognitive changes compared with dementia and this could possibly related to the length of exposure to the medications.

Implications for practice

Anticholinergic agents are one of the first-line option for pharmacological management of OAB, and the overall consensus based on the literature on the effects of these drugs on cognition and dementia raises the need for discretion when prescribing in certain patient groups (Box 1). Many

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physicians recognize that potential cognitive changes with these drugs are an important issue, but wide variation in knowledge and prescribing practises still occurs in response to this risk.[105] Good clinical practice dictates erring on the side of caution and avoiding OAB anticholinergic medications in patients with established cognitive impairment.[106] However, this advice does not mean that those patients with dementia and OAB should not be offered treatment for their bladder condition, as these conditions commonly coexist, and when they do they can be associated with an increased risk of fractures, urinary infections, and overall health care use.[107]

Researchers have reported on the clinical efficacy and safety of OAB anticholinergic therapy in patients with cognitive impairment or dementia[73,79,108]; however, prescribing these medications seems like an unnecessary risk as several non-anticholinergic based OAB therapies are now available, such as β-3 agonists, neuromodulation (including tibial, sacral, or pudendal), and intravesical botulinum toxin.[5,6] β-3 agonists are an oral medication that can be initiated by any health-care provider and, therefore, are particularly an attractive alternative. The role of β receptors in the brain is not fully understood[109], although a study of older patients (mean age 72) with OAB treated with the β-3 agonist mirabegron versus placebo did not show any significant change in cognitive impairment scores after 12 weeks of treatment (p=0.47)[110]. Additionally, the use of anticholinergics in patients with dementia who are treated with cholinesterase inhibitors is counterintuitive, and clinical studies have suggested that prescribing anticholinergics in these patients could accelerate functional decline.[111,112] If anticholinergic therapy is going to be considered in patients with cognitive impairment or dementia, the use of medications that have preferable physicochemical and pharmacodynamic properties, and prospective clinical data on cognitive effects (as with darifenacin and trospium) would seem most appropriate. Oxybutynin should be avoided in this patient population (as recommended by the United Kingdom National Institute for health and Care Excellence (NICE) guidelines on incontinence [113]); if absolutely necessary, a low-dose extended-release formulation should be used based on the data from a single randomised placebo controlled study of 50 women (age >65 years) in nursing homes.[73]

In patients over 65 years of age and patients with underlying cognitive impairment, or conditions that put them at risk of progressive cognitive impairment or dementia (such as subjective

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memory loss or being an APOE-ε4 carrier [114]), determining the degree of risk posed with OAB anticholinergics is a challenge. Healthy older people have age-related decline in neural cholinergic activity and mAchR density, and patients with brain injury from degenerative, vascular or inflammatory pathologies have impaired cholinergic networks.[115,116] These patients often have polypharmacy, which increases the chance of co-existing medications that have anticholinergic properties that are prone to drug-drug interactions.[85] Further research is required to understand which factors predict susceptibility to developing central adverse effects in these at-risk populations. Until then, sensible prescribing should include a review of the clinical need for instituting pharmacological intervention, considering non-anticholinergic OAB treatment alternatives and close monitoring of cognitive and functional performance should an selective anticholinergic agent be cautiously instituted. Notably, numerous drugs with anticholinergic properties (including over-the-counter medications), and over half of older patients take at least one anticholinergic medication.[89] Patients with an existing high anticholinergic burden should be identified, and the risks of additional anticholinergic medication carefully considered. In all patients the potential therapeutic benefit associated with effective OAB treatment should be weighed against the potential adverse effects of anticholinergic therapy.

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Future directions

Extensive research has been conducted on the topic of OAB anticholinergics and cognitive change, but important questions remain unanswered. Advanced techniques, such as functional MRI could help us to understand how oral OAB anticholinergics affect functional changes during cognitive tasks, and might offer insights into the reversibility of cognitive impairment from these medications.[117] An improved understanding of the effects of long-term OAB anticholinergic use on cognition is needed, and the magnitude of danger in at-risk populations requires more study with prospective clinical trials. Previous studies have identified differential magnitudes of risk between men and women for anticholinergic induced cognitive changes[100,118] (perhaps owing to the neuroprotective effect of oestrogen[119]), and this difference in outcomes should be explored prospectively. Other patient groups with inherent potential anticholinergic interactions, such as those with the APOE-ε4 allele could be studied by combining genetic registries with administrative data.

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OAB itself might be an early sign of neurodegeneration that precedes cognitive impairment[28,120]: this possibility underscores the importance of using equivalent, non-anticholinergic-treated populations with OAB as control groups in future studies. Future administrative data studies of OAB anticholinergics and dementia should exclude oxybutynin users or stratify results based on type of OAB anticholinergic used, as prospective clinical trials have shown that oxybutynin leads to cognitive impairment.[16,21,24,71,72,74] Finally, whether anticholinergic-related cognitive changes that are reversible with medication discontinuation lead to an increased risk of future cognitive impairment or dementia is unknown. This concept is particularly relevant as many people only use OAB anticholinergics for a short period of time[121] and, therefore, it would be reassuring to the physicians who prescribe these medications that any cognitive adverse effects are reversible.

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Conclusions

Short-term cognitive impairment has been well studied for most OAB anticholinergics, and in general, oxybutynin is the only medication with consistent negative effects. Large-scale observational studies generally support a link between anticholinergic use and dementia (including specifically OAB anticholinergics); however, residual confounding and conflicting results make a definitive conclusion about a causal relationship difficult. Selective use of anticholinergics with favourable physicochemical and pharmacodynamic properties and randomized trial evidence supporting cognitive safety could be appropriate in older patients and those at risk of cognitive impairment.

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Author contributions

B. W, K. R, and J. N. P. researched data for the article, made substantial contributions to discussion of its content, wrote, edited and reviewed the article prior to submission.

Competing interests

The authors declare no competing interests.

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Key points

1. Short-term randomized clinical trials (most < 4 weeks) have not shown substantial cognitive impairment with OAB anticholinergics other than oxybutynin.
2. Very few long-term clinical studies (>3 months) on OAB anticholinergics exist, and those studies that are available have conflicting results and are limited by methodological issues.
3. Large, observational studies of OAB anticholinergic use have shown that these medications are associated with an~ 20% increased relative-risk of dementia, but residual confounding and reverse-causality cannot be ruled out.
4. Alternative overactive bladder treatments might be more appropriate for patients over 65 years of age, and those patients with underlying mild cognitive impairment (or conditions that put them at risk of it); when necessary careful use of anticholinergics with favourable physicochemical and pharmacokinetic and pharmacodynamic properties and cognitive safety data could be considered.

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Table 1. Randomized controlled trials evaluating the short-term cognitive effect of various overactive bladder anticholinergics.

Medications	Study Design	Population	Outcome evaluation	Evaluation period	Results	Ref
Oxybutynin IR 5 or 10mg, Diphenhydramine 50mg, placebo	Randomized, double-blind, placebo-controlled, crossover study	Health older people (Mean age 69, 41% women, n=12)	Buschke Selective Reminding Test, Digit Span, Verbal Fluency-Letters, Trail-making Parts A and B, and Digit Symbol Substitution.	Single dose (single evaluation 90 mins after dose)	After correction for multiple comparisons, oxybutynin significantly impaired Buschke Long-Term Storage (p<0.01), Buschke Recall from Long-Term Storage (p<0.01), and Reaction Time scores (p<0.01) compared with placebo	71
Tolterodine 4mg IR, oxybutynin IR 15mg, trospium 45mg, placebo	Randomized, single-blind, parallel-group study	Healthy men (mean age n=64)	Quantitative-topographical EEG at rest, and during mental demand	Single day	Compared with placebo, tolterodine and trospium only decreased power in the θ frequency (p<0.05) Oxybutynin significantly decreased power in 4 out of 6 frequency bands (p<0.05)	72
Darifenacin CR 3.75 or 7.5 or 15mg, Darifenacin IR 15mg, placebo	Randomized, double-blind, placebo-controlled, three-period crossover study	Healthy older people (Mean age 71, 58% women, n=129)	Blessed Information-Memory Concentration test (attention, vigilance, memory and reaction time)	2 weeks (single evaluation at end of study)	No significant change in any of the cognitive measures with darifenacin compared with placebo (p>0.05)	22
Darifenacin CR 7.5 or 15mg, dicyclomine 80mg, placebo	Randomized, double-blind, placebo-controlled, four-period crossover study	Healthy young men (mean age 28, n=23)	Cognitive Drug Research computerised assessment system (ability to access short-term memory, to concentrate, and to respond rapidly)	1 week (serial evaluations over 12hrs on the 7th day)	Darifenacin produced no detectable effect on the cognitive tests throughout the 12 hours or with repeated testing on day 7 (p>0.05)	23

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Darifenacin 15mg, oxybutynin ER 15mg, placebo	Randomized, double-blind, double-dummy, placebo-controlled, parallel group study	Healthy older people (mean age 67, 62% women, n=150)	Psychologix and/or CogScreen computerized cognitive function tests (immediate or delayed memory recall, visual attention and memory, psychomotor or reaction time and information processing)	3 weeks (evaluation at the end of study)	No significant difference between darifenacin and placebo with memory (delayed and/or immediate recall) (p>0.05). Oxybutynin was associated with a significant deterioration (p=0.01) compared to placebo	[16]
Oxybutynin ER 5mg, placebo	Randomized, double-blind, placebo-controlled trial	Cognitively impaired women in a nursing home (mean age 88, n=50)	CAM, MMSE, SIB, and Brief Agitation Rating Scale	4 weeks (evaluation at the end of study)	No significant differences in cognitive outcomes with oxybutynin compared with placebo (p>0.05), and no cases of delirium.	[73]
Solifenacin 10mg, Oxybutynin IR 10mg, Placebo	Randomized, double-blind, placebo-controlled, three-period crossover study	Healthy older people (Mean age 69, 50% women, n=12)	Cognitive Drug Research computerized assessment system (measures attention, vigilance, working memory, episodic memory and speed of memory)	Single dose (Serial evaluations over a 24hr period)	No statistically significant change with solifenacin compared with placebo (p>0.05). Oxybutynin IR led to a statistically significant impairment of Power of Attention (p=0.02), Continuity of Attention (p<0.02), Quality of Working Memory (p<0.01) and Self-rated Alertness (p=0.02)	[24]
Oxybutynin gel 10%, Oxybutynin IR 15mg, placebo	Randomized, double-blind, placebo-controlled trial	Healthy older people (mean age 68, 65%	Psychologixa Test Battery (Name–Face Association Test, Misplaced Objects Test and Face Recognition Test) and subtests from	1 week (evaluation at the end of study)	No significant difference between oxybutynin 10% gel and placebo (p>0.05)	[74]

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		women, n=152)	the CogScreen test battery (matching to sample test, visual sequence comparison test, symbol digit coding test, and divided attention test-visual monitoring response time)		Significantly lower score on Misplaced Objects Test with oxybutynin IR 15mg than placebo (p=0.03).	
Solifenacin 5mg, oxybutynin IR 5mg, placebo	Randomized, double-blind, placebo-controlled, three-period crossover study	Older people with mild cognitive impairment (mean age 79, 46% women, n=26)	Cognitive drug research computerized assessment system (attention tasks, simple reaction time, digit vigilance, choice reaction time, working memory tasks, numeric working memory, spatial working memory, episodic secondary memory tasks, immediate word recall, delayed word recall, word recognition, and picture recognition)	3 weeks (serial evaluations after the final dose)	No significant difference between solifenacin and placebo in the cognitive measures (p>0.05). Oxybutynin significantly decreased both power (p=0.04) and continuity of attention (p=0.002) versus placebo at 1–2 h after administration.	[21]
Fesoterodine 4 or 8mg, alprazolam, placebo	Placebo-controlled, double-blind, double-dummy crossover study	Healthy older people (65-85 years of age, n=20)	CogState and the RAVLT	1 week (evaluation at the end of the study)	No significant change in any of the cognitive measures compared with placebo (p>0.05).	[25]
Trospium ER 60mg, placebo	Randomized, double-blind, placebo-controlled trial	Healthy women (mean age 68, n=45)	Hopkins Verbal Learning Test-Revised, MMSE, digit span, Trails A & B.	4 weeks (evaluation at the end of study)	No change in cognitive function with trospium compared with placebo (p>0.05).	[26]
Solifenacin 20mg + trospium 60mg, Solifenacin 10mg + trospium 30mg, placebo	3-arm randomized clinical trial	Healthy older women (mean age 69, n=312)	MMSE, Controlled Oral Word Association Test, Wechsler Adult Intelligence Scale-Revised, Wechsler Memory Scale III, Colour Trails Test, and California Verbal Learning Test scales	8 weeks (single evaluation at end of study)	No difference in any cognitive parameters compared with placebo (p>0.05).	[27]

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CAM, Confusion Assessment Method; CR, controlled release; ER, extended release; IR, immediate release; MMSE- Mini-mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; SIB, Severe Impairment Battery

Table 2. Studies examining overactive bladder anticholinergic use and long-term cognitive decline

Study design	Population	Outcome	Evaluation Period	N prescribed OAB anticholinergics	Results	Ref
Prospective cohort study	Geriatric outpatient clinic in Turkey (mean age 74, 92% women)	MMSE	6 months	140	Significant mean decline of 0.4 MMSE points for 50 patients taking darifenacin (p=0.04). Non-significant MMSE decline of 0.2 points for 43 oxybutynin initiators (p=0.32). No change in MMSE for 26 trospium initiators (p=0.93). 0.1 point increase in MMSE for 21 tolterodine (p=0.63) initiators, compared with 28 patients in the exercise group with no change in MMSE (p=0.72).	[79]
Prospective cohort study	Urogynecology centre in the US (mean age 77, 100% women)	MOCA	12 months	60	Non-significant mean 0.37 point greater decline in MOCA in 59 women prescribed oxybutynin or 1 woman prescribed trospium than 46 women in the control group (p=0.53). However, when excluding those with neurological disease, this mean decline in MOCA was only 0.15 points greater in 50 oxybutynin or trospium users than the control group.	[78]
Retrospective cohort study	NACC cohort – participants with normal cognition in the US (mean age 77, 58% women)	MMSE	12 months	259	Adjusted OR of 1.26 (95% CI 0.99–1.62) for any decline in MMSE for 259 new OAB anticholinergic users compared with 3,269 non-users.	[80]

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					Adjusted OR of 1.42 (95% CI 1.05–1.92) for any decline in MMSE for non-selective agent use compared with no-use.	

CI, confidence interval; MMSE = Mini–Mental State Examination, MOCA = Montreal Cognitive Assessment, NACC = National Alzheimer's Coordinating Center; OR, odds ratio

Table 3. Observational studies that examine overactive bladder anticholinergic use and dementia incidence

Study design	Data source	Mean age, years	% Male	Study duration, years	N prescribed OAB anticholinergics	Multivariable regression adjusted results		Ref
Retrospective cohort study	US Medicare database	76	21%	1–9	71,668	No difference between M3-selective and non-selective medications and risk of dementia. OR (95% CI) for dementia compared with 1–364 TSDDs of any non-selective OAB anticholinergic:		[99]
						366–729 TSDDs	1.05 (0.99–1.10)	
						730–1094 TSDDs	1.11 (1.05–1.17)	
						>1094 TSDDs	1.10 (1.04–1.15)	
Subgroup analysis of case-control study	UK primary care database (Qresearch)	76	37%	1–11	25,642	OR (95% CI) for dementia compared with patients without OAB anticholinergic prescription:		[14]
						1–90 TSDDs	1.19 (1.13–1.26)	
						91–365 TSDDs	1.35 (1.27–1.45)	
						366–1095 TSDDs	1.65 (1.53–1.78)	
						>1095 TSDDs	1.65 (1.56–1.75)	
Subgroup analysis of retrospective cohort study	Taiwan National Health Insurance Research Data set	64	51%	2–15	4,542	HR (95% CI) for dementia of 1.13 (0.93–1.23) for OAB anticholinergic prescription compared with none.		[92]
Subgroup analysis of case-control study	UK primary care database (Clinical Practice Research Datalink)	71	37%	4–20	20,134	OR (95% CI) for dementia of 1.18 (1.13–1.23) for OAB anticholinergic prescription compared with none. OR (95% CI) by cumulative DDDs compared with no prescription:		[15]
						1–13 DDDs	1.02 (0.90–1.15)	
						14–89 DDDs	1.10 (1.03–1.17)	
						90–364 DDDs	1.21 (1.12–1.31)	
						365–1459 DDDs	1.35 (1.24–1.46)	

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						≥1460 DDDs	1.24 (1.07–1.44)	
Retrospective cohort study of adults with LUTS	Taiwan National Health Insurance Research Data set	66	84%	1–12	2,731	HR (95% CI) for dementia compared with <28 DDDs.		[97]
						28–84 DDDs	0.88 (0.73–1.06)	
						85–336 DDDs	1.15 (0.97–1.37)	
						≥337 DDDs	1.40 (1.12–1.75)	
Retrospective cohort study of adults without depression	Ontario, Canada Health administrative databases	73	56%	0–3	47,324	HR (95% CI) for dementia of 1.23 (1.12–1.35) for OAB anticholinergic prescription compared with 23,662 patients prescribed mirabegron.		[122]
Retrospective cohort study of adults with diabetes	Taiwan National Health Insurance Research Data set	62	64%	0.5–6	7,620	HR for dementia compared with 2,540 diabetic non-users matched on age, sex and year:		[98]
						Oxybutynin	2.35 (1.96–2.81)	
						Solifenacin	2.16 (1.81–2.58)	
						Tolterodine	2.24 (1.85–2.73)	

CI, confidence interval; DDD, Defined Daily Dose; HR, hazard ratio; LUTS, Lower urinary tract symptoms; OAB, overactive bladder; OR, odds ratio; TSDD, total standardized daily doses

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Figure 1. Distribution and general role of the muscarinic acetylcholine receptors (mAchRs) **in the human body and brain.**

mAchRs are located in several organs (such as the brain, heart, lungs, bowel and bladder). In the brain, the major cholinergic pathways are the basal forebrain, including the basal nucleus complex and medial septa group, and pontine cholinergic system, which project to different areas in the thalamus and cortex. mAchRs have five sub-types that have various roles: M1 receptors are concentrated in the central nervous system (CNS), M2 receptors in the heart, and M3 receptors in smooth muscle. M4 and M5 receptors are located primarily in the CNS, but their exact role is unknown.

Figure 2. Anatomy of the blood-brain barrier (BBB), and how certain anticholinergics interact with it.

The BBB protects the central nervous system by preventing toxins from entering, and maintaining the ionic balance around the neurologic tissue. It is composed of capillary wall endothelial cells and astrocyte feet that encircle the capillary, and pericytes within the basement membrane of the capillary. Physicochemical properties such as size, lipophilicity and the charge of anticholinergic drugs influence their ability to cross the BBB. For example, oxybutynin is a neutral compound that is lipophilic, properties that facilitate passive diffusion across the BBB, whereas trospium has a charge and is poorly lipohilic and 5-HMT (prodrug of fesoterodine) and darifenacin are poorly lipohilic and are larger in size. Active transport mechanisms (such as the P-gp protein) actively move some anticholinergic drugs (such as 5-HMT, darifenacin and trospium) out of the brain.

Box 1| Considerations for the treatment of patients with overactive bladder (OAB) with varying cognitive risk profiles based on the available evidence

Normal cognition aged<65 years

Consider OAB anticholinergics or β-3 agonists as therapeutic options for OAB.

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Deleted: [Au: Can you start by explaining what the BBB is and what its function is please?]

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Commented [BW8]: No reference, this is based on the synthesis of the available evidence.

Deleted: [Au: Is there a reference for this? I know the formatting looks strange, but [bH1] etc are for the production team to put into a box figure].

Normal cognition aged >65 years

Consider a trial of β-3 agonists as initial oral medical therapy if medically appropriate.
Avoid oxybutynin in most cases. If required, use low-dose, extended release formulations.
Consider OAB anticholinergics with preferable physicochemical and clinical cognitive safety evidence (such as darifenacin, trospium or fesoterodine) as oral therapy options for OAB if medically appropriate.

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Potential at-risk groups [a]

Use a β-3 agonist as initial oral medical therapy for OAB if medically appropriate.
Avoid oxybutynin in most cases. If required, use low-dose, extended release formulations.
Consider OAB anticholinergics with preferable physicochemical and clinical cognitive safety evidence (such as darifenacin, trospium or fesoterodine) as oral therapy options for OAB if medically appropriate.
Consider whether alternative OAB treatment modalities (such as tibial nerve neuromodulation or intravesical botulinum toxin) might be preferable to OAB anticholinergic therapy.

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Documented cognitive impairment or dementia

Use a β-3 agonist as initial oral medical therapy for OAB if medically appropriate.
Avoid oxybutynin.
A low dose of an OAB anticholinergic with preferable physicochemical and clinical cognitive safety evidence (such as darifenacin, trospium or fesoterodine) can be considered as oral therapy options for OAB if medically appropriate and deemed to be important for the patient's quality of life.
Consider total anticholinergic medication burden.
Screen for subjective memory problems and falls.
Ask care givers to monitor for cognitive and functional changes. If possible, the clinician should use validated scales.
Consider whether alternative OAB treatment modalities (such as tibial nerve neuromodulation or intravesical botulinum toxin) might be preferable to OAB anticholinergic therapy.

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[f] [a]At risk groups include patients with neurological disorders at risk of developing cognitive impairment and those with frailty or suspected mild cognitive impairment

Glossary

Protopathic bias (also known as reverse causality): when a medication is initiated to treat the initial symptoms of an undiagnosed disease.

Striatal mAChR: Muscarinic acetylcholine receptors within the striatium of the brain (a subcortical structure within the forebrain that makes up the basal ganglia).

Efflux transporter proteins: active transporters than move toxic substances out of cells.
name-face association test: A cross-modal associative memory test. It uses 16 face-name pairs and 16 face-occupation pairs, and the person has to try and remember different pairs, during both the immediate and the delayed (30 minutes later) tests.

EEG frequency bands: Electroencephalogram readings can be decomposed into different component frequencies (delta, theta, alpha, beta, and gamma), which are associated with specific functional characteristics.

Mini-mental state examination: a standardised and widely used test of cogntivive function for adults. It evaluates orientation, attention, memory, language and visual-spatial skills.
selective serotonin reuptake inhibitors: medications which inhibit the reabsorption of serotonin into neurons, which can help with psychiatric problems such as depression and anxiety.

Cholinesterase inhibitors: These medications prevent the breakdown of acetylcholine, and can improve intracellular communication and treat symptoms of dementia.

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Blayne- the editor requested that we strengthen this section on mechanisms of cognitive decline. The arguments were scattered about and so have restructured this section:
-ACs result in reduced cholinergic activity
However other factors influence whether this can result in cognitive decline
-possible susceptibility biomarkers
-length of exposure
-AC burden
-Imaging and pathological changes

Once we have discussed the central impact of ACs and evidence and possible risk factors then ending on the pharmacodynamic properties of ACs and how this may also influence the occurrence of cognitive functions (and hence this section has now been moved down)

I can see that the editor had moved the BBB section up, however in the proposed restructure of this section I wonder whether it would best be placed at the end.

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I can see that the abbreviation has been expanded further down

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The subtitle can probably go if you agree as it becomes one single section exploring risk factors for developing cognitive dysfunction

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While I appreciate you would prefer p values, to explain all of these numbers and p values would take an entire page. These tests have several numerical results with different p-values for each. I do not think the reader will get anything from these numbers, as they represent specialised scales and are not readily interpretable like risk ratios.

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