

## **The cognitive impact of anticholinergics for overactive bladder patients**

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## **Abstract**

Overactive bladder (OAB) is often treated with medications with anticholinergic properties. The impact of this medication class on cognition and risk of dementia has been a frequent topic of study. Short-term randomised trials have demonstrated that oxybutynin leads to impaired memory and attention, however trials involving other OAB anticholinergics have not been shown to have significant impacts on short-term cognitive function. In contrast, large, population-based studies have generally found significant associations between anticholinergic medications (including those that studied OAB anticholinergics exclusively) and dementia. These studies must still be interpreted in the context of potential residual confounding (where increased OAB medication use due to prodromal urinary symptoms associated with dementia leads to the observed risk increase). The discordant results between short-term cognitive safety and long-term increased dementia risk may be explained by a high proportion of oxybutynin users in the dementia studies, or a study duration that was too short in the prospective clinical trials. When necessary, the cautious use of selected OAB anticholinergic agents with favorable physicochemical and pharmacokinetic properties and clinical trial evidence of cognitive safety may be appropriate in those with potential risk factors for cognitive impairment.

## Key points

1. Short-term randomised clinical trials (most less than 4 weeks) have not shown significant cognitive impairment with OAB anticholinergics other than oxybutynin.
2. There are very few long-term clinical studies (>3 months) on OAB anticholinergics and those that are available have conflicting results and are limited by methodological issues.
3. Large observational studies of OAB anticholinergic use have shown they are associated with an approximately 20% increased relative risk of dementia, but residual confounding and reverse-causality cannot be ruled out.
4. Elderly patients, and those with underlying mild cognitive impairment (or conditions that put them at risk for it) may be best served with alternative overactive bladder treatments; when necessary careful use of anticholinergics with favorable physicochemical and pharmacokinetic properties and cognitive safety data may be considered.

## Introduction

Overactive bladder (OAB) is a common condition that affects approximately 10-15% of the population, is more common as people age, and accounts for billions of dollars of direct and indirect costs.<sup>1,4</sup> In general it is a chronic condition, with only a small proportion of patients experiencing spontaneous remission of their symptoms.<sup>2,2</sup> The understanding of the etiology of OAB has progressed in the last few decades, and several potential OAB phenotypes and pathologic mechanisms have been identified.<sup>3,3</sup>

The management of OAB has been well outlined in societal guides, such as those from the American Urology Association<sup>4</sup> and European Association of Urology<sup>5</sup>. In general, they recommend initial conservative interventions and lifestyle modification strategies, and then a trial of medical therapy for patients with bothersome symptoms. The first drug therapy for OAB was anticholinergic medications, such as oxybutynin (approved in the 1970's). With time, several additional medications (such as tolterodine, trospium, darifenacin, solifenacin, and fesoterodine) with various pharmacodynamic properties (but all considered part of the anticholinergic class) were developed and approved for use in OAB patients.<sup>6</sup> All of these medications have similar efficacy, with metaanalyses suggesting an average reduction of 0.5-1.0 episodes of incontinence per day, 0.5-1.3 fewer micturition's per day and, and 0.6 to 1.5 fewer episodes of urgency per day<sup>7,8</sup>; in a high quality randomised study including an arm treated with solifenacin, the cure rate for urinary incontinence was 13%.<sup>9</sup> Long-term adherence to therapy is modest, with only 10-40% of people continuing with medical therapy after a year.<sup>10</sup> This limited persistence is due in part to the side effects associated with anticholinergic medications, which include gastrointestinal, ocular, urinary tract, neurologic, and cardiovascular effects.<sup>11</sup> While many of the specific side effects (such as dry mouth and constipation) are well recognised potential adverse effects of these medications, cognitive symptoms and increased dementia risk have been increasingly linked to medications with anticholinergic properties. Large population-based observational studies have demonstrated that exposure to anticholinergic medications may increase the risk of dementia<sup>12,13</sup>, and

even exposure to a few weeks of oxybutynin has been shown to be associated with measurable cognitive impairment.<sup>14,14</sup> These neurological effects are particularly relevant, as they can result in significant loss of independence, are associated with morbidity, and have substantial societal and healthcare costs.<sup>15,16,15,16</sup> From a patient perspective, cognitive impairment is the most unwanted anticholinergic side effect.<sup>17,17</sup>

While guidelines<sup>4,5,4,5</sup> do mention cognitive impairment as a potential consideration, only the American Urogynecology Society has specifically addressed this topic in relation to OAB.<sup>18,18</sup> There are some challenges in addressing cognitive impairment and OAB anticholinergics: smaller randomised trials examining short term cognitive function suggest several of the OAB anticholinergics are safe<sup>19,19</sup>, many of the large observational studies showing an increased risk of dementia with anticholinergics are not exclusive to the OAB population<sup>12,13,12,13</sup>, and these studies may have been susceptible to protopathic bias. Lower urinary tract symptoms (including urinary urgency, the hallmark of OAB) often predate the appearance of neurologic symptoms of cognitive impairment or dementia<sup>20,20</sup>, this can lead to a biased risk assessment in observational studies, whereby the association between anticholinergic medications and cognitive outcomes is due to OAB being a prodromal syndrome for cognitive impairment or dementia.

There is a need for physicians who treat OAB to understand the potential cognitive risks associated with anticholinergic therapy and be able to weight the risks and benefits associated with the long-term use of these medications. The purpose of this review is to summarise the mechanisms by which OAB anticholinergics may impact cognition/dementia risk, and review and critique the clinical evidence specifically related to OAB anticholinergics.

## **Central Nervous System effects of Anticholinergic Agents**

### *Distribution of cholinergic receptors*

In the 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. The cholinergic neural circuitry plays different vital roles ranging from higher-level functions such as learning, memory, attention, sensorimotor processing, to lower-level functions such as sleep-wake cycles and arousal.<sup>21-23,24-25</sup> M1, M2 and M4 mAChRs are expressed in most brain regions<sup>23,24,23,24</sup> and the M1 receptor is highly expressed throughout the hippocampus<sup>25,25</sup> and the frontal, temporal, parietal, and occipital neocortices, followed by M2 and M4 subtypes<sup>26,26</sup> (figure 1). Striatal mAChR levels are among the highest in the CNS<sup>27,27</sup> and M1 and M4 are the most abundant subtypes. This is in contrast to the LUT, where the most widely distributed muscarinic receptor is the M3 subtype, though the M2 receptor is functionally most relevant.

#### *Anticholinergic mediated mechanism of cognitive decline*

Clinical studies suggest that the ability of certain anticholinergic medications to exert CNS effects is due to antagonism of the M1 subtype, and to an extent M2 and M4 receptors, resulting in a decline in central cholinergic activity and cognitive dysfunction, particularly memory loss.<sup>28-30,28-30</sup> A preliminary study suggested that carriers of the APOE-ε4 allele have an increased sensitivity to anticholinergic treatment-induced memory deficits, and this may reflect decreased cholinergic function or reserve.<sup>31,31</sup> The presence of CSF Alzheimer's disease biomarkers (tau and abeta) have also been shown to increase susceptibility to developing mild cognitive impairment.<sup>32,32</sup> Cognitive side effects with bladder medications have been reversed on cessation of the drug<sup>33,33</sup>, and whether length of exposure to medications or extent of anticholinergic burden can influence reversibility following cessation is not known.

#### *Anticholinergic Burden*

Cumulative anticholinergic exposure, called the anticholinergic burden, has been linked to a number of adverse outcomes such as cognitive impairment, greater falls risk, hospitalisation and death.<sup>34,35</sup> To date, eighteen different anticholinergic burden scales have been designed that quantify the cumulative exposure to anticholinergic activity. However a considerable heterogeneity exists between scales: they measure anticholinergic burden differently based on expert opinion, clinical anticholinergic effects or in vitro testing, they use different scoring

systems and have been applied in different clinical settings.<sup>3636</sup> One review of anticholinergic burden scales in patients with dementia found the prevalence of anticholinergic use varied between 36-69% depending upon which scale was used.<sup>3737</sup> There is no gold standard to determine how “strong” an anticholinergic effect a medication has, or how to best assess the total anticholinergic burden a patient may be exposed to. The association between adverse outcomes and anticholinergic burden varies between scores and has not been conclusively established, however, all bladder anticholinergic agents are consistently ~~scored~~ considered strong anticholinergics high in terms of anticholinergic effects.<sup>3636</sup>

*Pathologic and neuroimaging evidence of negative cognitive effects from anticholinergic medications*

Histologic and neuroimaging studies have demonstrated associations between structural changes and anticholinergic medication exposure. In community-dwelling older adults, midlife exposure to anticholinergic medications has been associated with greater rates of atrophy in total cortical grey matter volume<sup>3838</sup>. In the cognitively normal elderly, use of anticholinergic medications has been shown to be associated with increased brain atrophy particularly in the temporal lobe.<sup>3939</sup> 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, and greater pathology was seen in the brains of Parkinson’s disease (PD) patients using anticholinergics compared to patients not receiving anticholinergics<sup>4040</sup>, though this has not been seen in studies evaluating non-PD brains.<sup>41,4241,42</sup>

A functional MRI imaging study in healthy (non-OAB) elderly adults (mean age 74 years) demonstrated that scopolamine (a medication with strong anticholinergic side effects) significantly reduced scores on the Buschke Selective Reminding Task correlated with reduced neural connectivity in different cortical networks.<sup>43</sup> A randomised trial of hypnosis or anticholinergic medications in patients with OAB showed that hypnosis resulted in increased functional connectivity of the dorsal attentional network in patients treated with hypnosis.<sup>44</sup>



### Pharmacodynamic properties of OAB anticholinergics

In order for anticholinergic medications to influence cognition, they must be able to directly interact with the central nervous system (CNS). This interaction is influenced by their pharmacodynamic properties (which determine their ability to cross the blood-brain barrier (BBB)) and the distribution of muscarinic acetylcholine receptor receptors (mAChR) subtypes in the CNS.

The penetration of drugs into the CNS is determined by permeability across the BBB, which is constituted by specialized endothelial cells of the capillary walls supported by a basal membrane, pericytes and astrocytic end-feet. The presence of tight (zonulae occludens) and adherens junctions interfere with paracellular transport, and the BBB regulates the transport of molecules between the vascular spaces and brain parenchyma.<sup>45</sup> Drugs that freely cross the BBB would be expected to attain high concentrations within the brain<sup>46</sup>, 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).<sup>47</sup> Amongst anticholinergic agents used for OAB, those with greater molecular weight such as darifenacin and 5-hydroxymethyl tolterodine (5-HMT, the active metabolite of fesoterodine), or those having hydrophilic properties due to the presence of a quaternary amine group that is ionized at physiological pH (such as trospium) are expected to therefore be less permeable across the BBB.<sup>46,48</sup> Efflux transporter proteins on the BBB can influence drug entry into the CNS; the best studied protein is P-glycoprotein (P-gp) present on the basolateral membrane of capillary endothelial cells.<sup>49</sup> Substrates with an affinity for the P-gp efflux transporter, such as 5-HMT, darifenacin and trospium, are actively expelled from the CNS.<sup>46,50</sup> However certain medications, such as statins and proton pump inhibitors can decrease the activity of the P-gp efflux transporter, and there are various genetic variations in the structure of the P-gp protein that affect its function.<sup>51</sup>

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.<sup>4644</sup> Moreover, drugs such as 5-HMT (the active metabolite of fesoterodine) have been shown to be associated with considerable central anticholinergic activity in in vitro brain tissue, while others such as darifenacin have low binding affinity (likely due to its M3 selectivity).<sup>5250</sup> Consistent with this result, positron emission tomography in a rat model demonstrated that muscarinic receptor antagonism in the CNS was highest with oxybutynin, and lowest with darifenacin.<sup>5354</sup>

The implications of these observations for humans is however uncertain. Increasing age, use of certain medications and presence of illnesses such as diabetes, neurological disease and stress can influence passive permeability and active transport mechanisms across the BBB.<sup>54,5552,53</sup> Therefore in human subjects, particularly those with relevant co-morbid diseases (which includes the vast majority of patients with OAB<sup>5654</sup>), all anticholinergic agents should be considered to have the potential to cross the BBB.

Some anticholinergic agents have a greater affinity for the M2/3 receptors compared to the M1 and may have more selective effects on the LUT sparing the CNS (for example darifenacin).<sup>4644</sup> Most other OAB anticholinergics are non-selective (oxybutynin, tolterodine, fesoterodine), or only weakly selective (solifenacin) for the bladder related muscarinic receptors.<sup>46,5744,55</sup>

### **Clinical evidence for OAB anticholinergic drugs and cognitive effects**

#### *Short-term cognitive effects*

In response to the concerns raised about cognitive changes from this class of medications, several randomised clinical studies have been carried out to assess the impact of OAB medications on cognition (Table 1). Most of these studies used a battery of validated neuropsychology tests that evaluated different cognitive areas including memory, attention, and executive functioning and were administered in a controlled and standardised setting after

use of specific medications of interest. The duration of therapy in these studies varied from a single dose of an OAB medication to eight weeks of regular therapy. Cognitive safety has been a frequently debated topic in the marketing of various OAB medications, and 9 out of 12 of the randomised trials referenced in table 1 were sponsored by pharmaceutical companies.

In one of the earliest randomised trials, oxybutynin was compared to diphenhydramine and placebo.<sup>58,56</sup> In this study involving healthy older people, 90 minutes after a single dose of oxybutynin there was significantly decreased memory and reaction times compared to placebo (and no change with diphenhydramine). Oxybutynin was also used as an active comparator (or positive control) in studies of other OAB medications because of its hypothesised significant cognitive effects.<sup>14,19,59,60,14,19,57,58</sup> Compared to placebo, oxybutynin significantly decreased scores on various outcomes such as memory tests<sup>14,59,14,57</sup>, measures of attention<sup>19,59,19,57</sup> and suppressed EEG readings<sup>60,58</sup>. As a surrogate for cognitive effects, rapid-eye movement sleep has also been shown to be impaired after a single dose of oxybutynin.<sup>61,59</sup> Oxybutynin was specifically studied in a small population of very elderly female nursing home residents with significant cognitive impairment.<sup>62,69</sup> Surprisingly, there was no difference in cognitive function compared to placebo at 4 weeks, however this may be because very low dosages were used (5mg extended release), or because the chosen outcome measures were not sensitive enough to detect change in patients with severe baseline impairment. Oxybutynin 10% gel did not significantly reduce scores on the name-face association test<sup>63,64</sup>, however neither did the active control of oxybutynin IR 15mg (although it did impact some of the other secondary cognitive outcomes).

The effect of tolterodine on neural activity was assessed using EEG.<sup>60</sup> A randomised trial was carried out with healthy (non-OAB) young males (18-35 years of age) who had an EEG performed after a single dose of oxybutynin, tolterodine, trospium, or placebo. While a single dose of oxybutynin significantly reduced the power in several EEG frequency bands, tolterodine had only a small effect on one frequency band.

Three randomised trials evaluating the M3 receptor selective drug darifenacin demonstrated that a range of different doses and formulations did not significantly impact different cognitive tests after 1 to 3 weeks of use in the healthy [\(non-OAB\) elderly \(>60 years of age\)](#) or in healthy [\(non-OAB\) young men \(19-27 years of age\)](#) compared to placebo.<sup>14,64,65</sup> Consistent with the hypothesis that Trospium should not be able to cross the blood-brain barrier, a study in healthy women showed there was no significant change in cognitive function after 4 weeks of treatment with 60mg of the extended release compared to placebo,<sup>66</sup> and even in combination with high doses of solifenacin, there was no measured cognitive impairment<sup>67</sup>. In keeping with the hypothesis that trospium should not cross the BBB, trospium was not detected in the CNS of healthy [\(non-OAB\) elderly \(65-75 years of age\)](#) volunteers,<sup>68</sup> and the use of trospium in patients with dementia and urge incontinence did not lead to a significant decline in cognitive scores after six months.<sup>69</sup>

A single dose of solifenacin did not significantly impact measures of cognition among a small group of healthy [\(non-OAB\) elderly \(65-75 years of age\)](#) patients<sup>59,57</sup>. After healthy [\(non-OAB\) elderly patients \(mean age 80 years of age\)](#) with mild cognitive impairment were treated for 3 weeks with solifenacin 5mg, there was no significant change in cognitive outcomes in a large randomised clinical trial.<sup>19,49</sup> Fesoterodine in both the 4mg and 8mg dose did not significantly impact the chosen cognitive outcomes after 1 week of therapy compared to placebo.<sup>70,68</sup>

Limitations in all of these randomised studies include that the patient populations were usually restricted to healthy [\(non-OAB\) elderly patients with no apparent cognitive impairment](#) (although clinical trials of oxybutynin<sup>62</sup> and solifenacin<sup>19</sup> were carried out in cognitively compromised populations). Second, the outcome measures used in these studies were quite variable, and difficult to compare across studies. Third, treatment periods were generally short, with 11 out of 12 of the randomised trials exposing patients to 4 weeks or less of OAB medication. Fourth, only half of the clinical trials<sup>14,19,60,63,64,70</sup> included an active comparator to ensure that the outcome measures and sample size were appropriate to detect cognitive changes. Finally, it is difficult to determine the clinical relevance of some of the deleterious

cognitive changes that were observed with oxybutynin, although the study by Kay et al compared the score change to that associated with normative aging changes, and found oxybutynin's negative effect was equivalent to 10 years of aging<sup>14</sup>.

#### *Long-term cognitive decline*

Three clinical studies that examined OAB anticholinergics and cognitive decline over a 6 or 12 month period are summarised in table 2. A prospective study followed women prescribed primarily oxybutynin.<sup>7169</sup> An unadjusted mean 0.37 point greater impairment in the Montreal Cognitive Assessment (MOCA) score ( $p=0.53$ ) was observed over 12 month compared to the control group. A greater relative decline (estimated mean 1.15 point greater impairment) was observed in the 10 women with neurological disease. However, the proportion of women completing the study was low (with about a 40% drop-out in each of the groups); this means that cognitive decline in the anticholinergic users may have been underestimated as those dropping out recorded lower cognition at baseline.

A study of 50 outpatients at a geriatric clinic in Turkey prescribed darifenacin observed an unadjusted 0.4 point greater decline in MMSE ( $p=0.04$ ) compared to 28 patients in the exercise group.<sup>7270</sup> However, some patients had neurological disease and 12% had dementia, and again a large proportion of patients discontinued therapy during the 6 months.

In retrospective analysis of data from the US National Alzheimer's Coordinating Center (NACC) cohort, an adjusted odds ratio of 1.26 (95% CI 0.99-1.62) was estimated for any decline in Mini-Mental State Examination (MMSE) scores over 12-months for 259 older adults with normal condition newly taking OAB anticholinergics compared to 3,269 non-users.<sup>73</sup> Analyses of crude MMSE change scores were not presented, but summary statistics suggest the mean decline in MMSE was negligible (0.04 points). An adjusted odds ratio of 1.42 (95% CI 1.05-1.92) was reported for any decline in MMSE for new users of non-selective agents.

These clinical studies do not support clinically relevant declines in cognition over 6-12 months with new OAB anticholinergic use in older adults with normal cognition and without neurological disease. However, the study estimates are likely biased due to poor long-term followup and treatment adherence. Furthermore, the MMSE score is not well-suited to identify mild cognitive impairment.<sup>74</sup> In contrast, observational studies examining all medications with anticholinergic properties find greater long-term decline in global cognitive measures in older people taking strong anticholinergics.<sup>75</sup> However, many of these studies also suffer from residual confounding and some of the medications could be prescribed for early symptoms of dementia.

#### **Clinical evidence for anticholinergic drugs and dementia risk**

##### *Population-based studies of anticholinergic medications in general*

Anticholinergic medications are commonly prescribed: around 10% of the older population regularly take medications with strong anticholinergic activity.<sup>76-78,74-76</sup> The most common of these is tricyclic antidepressants; antipsychotics, antihistamines, and medications for Parkinson's disease and OAB are also common. Many observational studies (which use routine electronic records to identify patients with dementia) report associations between the use of medications with strong anticholinergic activity and increased incidence of dementia, however study findings are heterogeneous and likely biased.<sup>75,73</sup> A recent meta-analysis estimated a pooled odds ratio (OR) of 1.20 (95% CI 1.09-1.32) for any strong anticholinergic use and incident dementia from seven studies, but with substantial heterogeneity.<sup>75,73</sup>

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 either risk factors for or early symptoms of dementia, such as depression, psychosis, and Parkinson's disease. Dementia has an insidious onset, and patients experience delays between recognizing and reporting symptoms and then being formally clinically diagnosed. It is estimated to take on average three years between onset of dementia

symptoms and record of a diagnosis in UK primary care.<sup>79</sup> A common methodological approach to handling latency periods is to apply a lag time to study follow-up and exclude any new dementia diagnoses in the first few years following the medication exposure.

In a recent systematic review, 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.<sup>7573</sup> Few studies accounted for confounding by the indications for anticholinergic medications and rarely were they able to account for confounding by underlying frailty. Many did not apply a lag time so are likely to be capturing prescribing to patients around the time the dementia diagnosis is being made. 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 report associations with strong anticholinergic use and increased incidence of dementia.<sup>12,13,80,8143,13,78,79</sup>

Consistent with a causal link, many studies also report greater associations with dementia incidence with longer exposure to anticholinergic medications. Pooled OR (95% CI) from meta-analysis estimated 1.23 (1.17-1.29) for incident dementia for  $\geq 90$  days use and 1.50 (1.22-1.85) for  $\geq 365$  days use (albeit with substantial heterogeneity for  $\geq 365$  days use).<sup>7573</sup>

The cognitive effect of anticholinergic medications was initially believed to be cumulative and additive, such that anticholinergic burden scores better quantify the overall risk of multiple simultaneous medications. However, there is little evidence that the cumulative use of drugs considered to have a low anticholinergic burden on these scales contribute towards any additional dementia risk.<sup>13,8213,80</sup> This is likely due to the poor evidence that these drugs have any clinically relevant anticholinergic properties.<sup>8381</sup>

Despite many studies observing associations with dementia, and evidence of dose-response effects, recent larger studies have pointed to inconsistencies in associations across drug classes contradicting a causal link.<sup>12,13,84</sup> Each of these studies report no associations between

strongly anticholinergic gastrointestinal drugs or antihistamines and incident dementia, which suggests either differential effects across different types of anticholinergic drugs or residual confounding with some of the other anticholinergic drugs (such as antidepressants, antipsychotics, Parkinson's Disease drugs) due to use for early symptoms of dementia. Few studies have examined anticholinergics and dementia risk in specific patient groups. For depression, one study found no difference in dementia incidence between US care home residents with depression using paroxetine (which has strong anticholinergic activity), compared to other SSRIs with little anticholinergic activity.<sup>85</sup> A US cohort study of community-dwelling older people prescribed antidepressants, also found no association with SSRIs or anticholinergic TCAs and dementia, however did report associations between paroxetine prescription and dementia.<sup>86</sup> In a cohort study in Taiwan of anticholinergics in Parkinson's Disease, ≥6 months exposure to Parkinson's Disease anticholinergics was associated with a HR (95% CI) of 1.23 (1.10-1.37) for incident dementia after a one year lag period.<sup>87</sup> The authors also demonstrated associations with dementia incidence for concomitant strong anticholinergic use from other classes. However, residual confounding is likely as the authors adjusted for only a small number of covariates. A cohort study of family practices in the Netherlands found no association with anticholinergic medication use and dementia when excluding antidepressants and antipsychotics.<sup>88</sup>

#### *Population-based studies of OAB anticholinergic medications*

To date, few studies have solely examined OAB anticholinergic use and dementia risk.<sup>89-92</sup> Some large studies examining anticholinergic medications in general have performed sub-group analyses by OAB anticholinergics.<sup>12,13,84</sup> These observational studies have been performed using either UK primary care databases, the Taiwan National Health Insurance Research Data set, Canadian data or US Medicare data and are described in table 3. It should be noted that these studies did not capture whether patients actually took the anticholinergic medications, but instead relied upon prescription refill or claims records.



Two large nested case-control studies were performed examining incident dementia using data from separate primary care practices in the UK.<sup>12,13</sup> Both reported sub-group analyses by drug class and by cumulative dose. Associations with increased incidence of dementia were observed with a greater cumulative dose of OAB anticholinergics (predominately oxybutynin and tolterodine), specifically with ORs greater than 1.20 once a standard dose was used for more than 90 days. Some associations reported in the study by Richardson et al were weaker than in Coupland et al, due to the application of a longer lag period and because medication exposure 4-20 years prior to dementia were examined (rather than 1-11 years prior for Coupland et al) and for adjustment of confounders at 4 years prior to dementia diagnosis, rather than at some time before the medication exposure.

Coupland et al also performed sensitivity analyses and observed similar associations between OAB anticholinergic prescription and dementia for men and women.<sup>12,13</sup> Observed associations were slightly greater for vascular dementia than Alzheimer's Disease, but this was not statistically significant. Associations were also slightly greater for dementia diagnosed before the age of 80 years. Associations were only marginally reduced when restricted to medication exposures occurring 5-20 years prior to dementia.

The findings from the subgroup analyses of these two studies should be interpreted with caution, as they likely suffer from residual confounding with the comparator group comprising the general older population not using OAB anticholinergic medications (and therefore less likely to have potentially prodromal bladder symptoms). It is also difficult to elucidate the timing of cause and effect and the timing of confounding effects in case-control studies.<sup>93,94</sup> However, these studies adjust for a wide range of confounders, and as both are consistent with each other this suggests 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).<sup>84,89,90</sup> Patients were followed, in general, from an earlier age (average 62-66 years) compared to the UK studies (average 71-76 years). Again, in subgroup analysis, Liu et al reported a hazard ratio (HR) for incident dementia of 1.13 (95% CI 0.93-1.23) for any OAB anticholinergic prescription compared to none.<sup>84</sup> Cumulative exposure was further explored by Wang et al and associations with greater dementia incidence was only observed for more than 12 months of OAB anticholinergic prescriptions with a reported HR (95% CI) of 1.40 (1.12-1.75).<sup>89</sup> A further matched cohort study from the same Taiwanese database but specifically evaluating patients with diabetes<sup>90</sup> reported a greater than 2-fold increased risk of dementia in the cohort exposed to oxybutynin, solifenacin, or tolterodine compared to no prescriptions for OAB medication. However, there was likely residual confounding as the comparator patients were not matched on their diabetes severity or their OAB status. Also, a short lag time (of only 6 months) may have led to over-estimated HRs. Although these studies were able to adjust for a wide range of health-related confounders, residual confounding is possible due to no information on smoking history and BMI. It should also be noted that there is likely significant overlap in the patients contributing to each of the three Taiwan studies as patient data was extracted from the same database.<sup>84,89,90</sup>

A recent retrospective cohort study examining US Medicare data reported no difference between M3-selective (darifenacin or solifenacin) and non-selective OAB medication and risk of dementia.<sup>91</sup> While darifenacin is quite selective for the M3 receptor, the findings could have been influenced by solifenacin showing much lower selectivity.<sup>57</sup> The authors also report small increased risks of dementia with greater than 2 years of exposure to any OAB anticholinergic compared to less than a year of use (ORs [95% CI] of 1.11 [1.05-1.17] and 1.10 [1.04-1.15] for use for greater than two and three years, respectively), but unfortunately did not compare to any shorter exposures. The study was methodologically limited by not accounting for mortality or censoring, being unable to determine the first OAB prescription timing and having variation in both the lag-times between exposure and dementia follow-up and timing of covariate measurement relative to the first OAB prescription.

Finally, a retrospective cohort study using Canadian linked administrative data reported a modest HR (95% CI) of 1.23 (1.12-1.35) for new OAB anticholinergic prescription and risk of dementia compared to first mirabegron prescription in older patients without depression.<sup>92</sup> 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]). One of the unique strengths of this study is the use of a matched comparison population which also had OAB, and had symptoms sufficient to also seek out medical therapy. This is important as OAB symptoms may be an early sign of undiagnosed cognitive diseases. Although matched on a wide range of confounders, the effects observed may be over-estimated due to no lag period, and alternatively under-estimated if clinicians were preferentially prescribing mirabegron to patients with cognitive impairment.

#### **The data in context**

When considering the literature on cognition and anticholinergic medications, it is important to differentiate between cognitive impairment and dementia. Dementia is usually defined as progressive cognitive impairment that is associated with functional impairment and loss of independence. Cognitive impairment usually refers to impairment of a single cognitive domain, which doesn't cause the degree of functional impairment that is associated with Dementia. While many patients with cognitive impairment will progress to dementia (estimates suggest 0.3-30% progress over two years), cognitive impairment can be reversible.<sup>95</sup> In the elderly, early cognitive changes and dementia likely exist on a spectrum of cognitive dysfunction, and the initial development, and then rate of progression is impacted by numerous variables. Cognitive impairment is a more insidious process; inhibition of cholinergic activity in neural networks involved in memory and attention plays a key role in the development of these early cognitive changes, however the precise mechanisms underpinning these changes remains unclear at present. In contrast, dementia is a well-characterised and defined disease condition with specific pathological changes that is not reversible.

Short-term clinical studies have not shown significant cognitive impairment with OAB anticholinergics other than oxybutynin (Table 1). Long-term clinical studies on OAB anticholinergics are lacking and those that are available are limited by methodologically issues (Table 2). [Cognitive impairment may be reversible or the patient may be able to compensate for these changes after a short period of impairment, and this may explain some of the differences between the short-term and long-term study results.](#) In contrast, a growing number of studies suggest a direct association between exposure to anticholinergic agents used for OAB symptoms and future dementia diagnosis (Table 3). Longer-term OAB anticholinergic use (in particular use for  $\geq 90$  days) is associated with an approximately 20% increased relative risk of dementia, but residual confounding and reverse-causality (where these medications are being prescribed for early symptoms or prodromes of dementia) cannot be ruled out. [These studies have been largely been carried out using administrative data, which cannot obtain a detailed cognitive evaluation at baseline, or a clinical diagnosis of dementia.](#)

The apparently discordant results between the prospective short-term clinical studies evaluating cognition, and the large observational studies evaluating dementia may be due to the high proportion of oxybutynin users in the OAB medication subgroups of the observational studies evaluating dementia risk. It is also possible that the short-term use of the newer OAB anticholinergics in the clinical trials (most of which were 4 weeks or less in duration) may not have been sufficient to lead to cognitive changes. The types of patients that receive anticholinergics in the real-world setting (and are the basis for the administrative data studies) are likely quite different from those in the prospective clinical trials on cognition. Many of the randomised clinical trials excluded the co-administration of other anticholinergic medications, which in the real-world setting may potentiate the effects of overactive bladder medications on cognition. Finally, OAB anticholinergic use may have a lower propensity to cause short-term cognitive changes as compared to dementia.

### **Implications for practice**

Anticholinergic agents are part of the first line option for pharmacological management of OAB, and the results of the literature on cognition and dementia with these medications raises the need for discretion when prescribing in certain patient groups (figure 3). While many physicians recognise this is an important issue, there is still wide variation in knowledge and prescribing practises in response to this risk.<sup>96</sup> Good clinical practice dictates erring on the side of caution and avoiding OAB anticholinergic medications in patients with established cognitive impairment.<sup>97</sup> However, this does not mean that those with dementia and OAB should not be offered treatment, as these conditions commonly coexist, and when they do it may be associated with an increased risk of fractures, urinary infections, and overall healthcare utilisation.<sup>98</sup> While authors have reported on the clinical efficacy and safety of OAB anticholinergic therapy in patients with cognitive impairment or dementia<sup>62,72,99</sup>, this seems like an unnecessary risk as there are now several non-anticholinergic based OAB therapies which can be considered such as beta-3 agonists, neuromodulation (including tibial, sacral, or pudendal), and intravesical botulinum toxin.<sup>4,5</sup> Beta-3 agonists are an attractive alternative, as they are an oral medication that can be initiated by any healthcare provider. While the role of beta receptors in the brain are not fully understood<sup>100</sup>, a study of older patients with OAB treated with mirabegron or placebo did not show any significant change in cognitive impairment scores after 12 weeks of treatment<sup>101</sup>. It is counterintuitive to use anticholinergics in patients with dementia who are treated with cholinesterase inhibitors, and clinical studies have suggested this may accelerate functional decline.<sup>102,103</sup> If anticholinergic therapy is going to be considered in patients with cognitive impairment or dementia, the use of medications which have both preferable physicochemical and pharmacokinetic properties, and prospective clinical data on cognition (such as darifenacin and trospium) would seem most appropriate. Oxybutynin should likely be avoided in this patient population (similar to the recommendation of the United Kingdom NICE guidelines on incontinence <sup>104</sup>); if absolutely necessary, a low dose extended-release formulation should be used.<sup>62</sup>

In elderly patients, and those with underlying cognitive impairment, or conditions that put them at risk for [progressive cognitive impairment or dementia](#) (such as [subjective memory loss or known APOE-ε4 carrier](#) <sup>105</sup>), it is more challenging to determine the degree of risk posed with OAB anticholinergics. The healthy elderly have age-related decline in neural cholinergic activity and muscarinic receptor density, and patients with brain injury from degenerative, vascular or inflammatory pathologies have impaired cholinergic networks. They often have polypharmacy, which increases the chance of coexisting medications with anticholinergic properties and are prone to drug-drug interactions. Further research is required to understand which factors predict susceptibility to developing central side effects in these at-risk populations. However, until then the cautious use of selected OAB anticholinergic agents and sensible prescribing would 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 anticholinergic agent be instituted. There are numerous drugs with anticholinergic properties (including over the counter medications), and over half of elderly patients take at least one anticholinergic medication.<sup>82</sup> Patients with an existing high anticholinergic burden should be identified, and the risks of additional anticholinergic medication carefully considered. In all cases, the potentially therapeutic benefit associated with effective OAB treatment should be weighed against the potential adverse effects of anticholinergic therapy.

### **Future Directions**

While much research has been conducted on the topic of OAB anticholinergics and cognitive change, there are still important unanswered questions. Advanced techniques such as [functional MRI](#) may help understand how [oral OAB anticholinergics impact functional changes during cognitive tasks, and may offer insights into the reversibility of cognitive impairment from these medications](#).<sup>106</sup> A better understanding of the impact of long-term OAB anticholinergic use on cognition is needed, and the magnitude of danger in at-risk populations requires more study. Previous studies have identified differential magnitudes of risk between men and women for anticholinergic induced cognitive

changes<sup>92,107</sup> (perhaps due to the protective effect of estrogen<sup>108</sup>), and this should be explored prospectively. Other groups with potential interactions with anticholinergic use, such as those with APOE-ε4 allele could be explored by combining genetic registries with administrative data. [OAB itself may be an early sign of neurodegeneration that precedes cognitive impairment<sup>20,109</sup>; this underscores the importance of using equivalent non-anticholinergic-treated OAB populations 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. Finally, whether anticholinergic-related cognitive changes that are reversible with medication discontinuation leads to an increased risk of future cognitive impairment or dementia is unknown. [This is particularly relevant as many people only use OAB anticholinergics for a short period of time<sup>110</sup>, and therefore it would be reassuring to physicians that trial these medications.](#)

## 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 OAB anticholinergics specifically), however residual confounding and some conflicting results make a definitive conclusion about a causal relationship difficult. Selective use of anticholinergics with favorable physicochemical properties and randomised trial evidence supporting cognitive safety may be appropriate in elderly patients and those at risk of cognitive impairment.

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

**Figure 2. Anatomy of the blood brain barrier, and how certain anticholinergics interact with it.**

**Figure 3. Considerations for the treatment of OAB patients with varying cognitive risk profiles based on the available evidence.**



**Table 1. Randomised controlled trials evaluating the short-term cognitive impact of various OAB anticholinergics.**

Study	Medications	Study Design	Population	Outcome	Evaluation period	Results
Katz, 1998	Oxybutynin IR 5/10mg, Diphenhydramine 50mg, placebo	Randomised, double blind, placebo controlled, crossover study	Health elderly (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, Buschke Recall from Long-Term Storage, and Reaction Time scores compared to placebo.
Todorova, 2001	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 to placebo, tolterodine and trospium only decreased power in the theta frequency. Oxybutynin significantly decreased power in 4/6 frequency bands.
Lipton, 2005	Darifenacin CR 3.75/7.5/15mg, Darifenacin IR 15mg, placebo	Randomised, double blind, placebo controlled, three period crossover study	Healthy elderly (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 to placebo.
Kay, 2005	Darifenacin CR 7.5/15mg, dicyclomine 80mg, placebo	Randomised, 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.
Kay, 2006	Darifenacin 15mg, oxybutynin ER 15mg, placebo	Randomised, double blind, double dummy, placebo controlled, parallel group study	Healthy elderly (mean age 67, 62% women, n=150)	Psychogix/CogScreen computerised cognitive function tests (immediate/delayed memory recall, visual attention and memory, psychomotor/reaction time and information	3 weeks (evaluation at the end of study)	No significant difference between darifenacin and placebo with memory (delayed/immediate recall), however oxybutynin was associated with a significant

				processing)		deterioration.
Lackner, 2008	Oxybutynin ER 5mg, placebo	Randomised, double-blinded, placebo-controlled trial	Cognitively impaired women in nursing home (mean age 88, n=50)	Confusion Assessment Method (CAM), Mini-Mental State Examination (MMSE), Severe Impairment Battery (SIB), and Brief Agitation Rating Scale	4 weeks (evaluation at the end of study)	No significant differences in cognitive outcomes with Oxybutynin compared to placebo, and no cases of delirium.
Wesnes, 2009	Solifenacin 10mg, Oxybutynin IR 10mg, Placebo	Randomised, double blind, placebo controlled, three period crossover study	Health elderly (Mean age 69, 50% women, n=12)	Cognitive Drug Research computerised 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. Oxybutynin IR led to a statistically significant impairment of Power of Attention, Continuity of Attention, Quality of Working Memory and Self-rated Alertness.
Kay, 2012	Oxybutynin gel 10%, Oxybutynin IR 15mg, placebo	Randomised, double-blinded, placebo controlled trial	Healthy elderly (mean age 68, 65% women, n=152)	Psychologica Test Battery (Name-Face Association Test, Misplaced Objects Test and Face Recognition Test) and subtests from the CogScreen test battery (matching to sample test, visual sequence comparison test, symbol digit coding test, and divided attention test-visual monitoring response time)	1 week (evaluation at the end of study)	No significant difference between Oxybutynin 10% gel and placebo, however there was a significantly lower score on Misplaced Objects Test with oxybutynin IR 15mg compared to placebo.
Wagg, 2013	Solifenacin 5mg, oxybutynin IR 5mg, placebo	Randomised, double blind, placebo controlled, three period crossover study	Elderly with mild cognitive impairment (mean age 79, 46% women, n=26)	Cognitive drug research computerised assessment system (attention tasks, simple reaction time, digit vigilance, choice reaction time, working memory tasks, numeric working memory, spatial working	3 weeks (serial evaluations after the final dose)	No significant difference between solifenacin and placebo in the cognitive measures, however, oxybutynin significantly decreased both power and

				memory, episodic secondary memory tasks, immediate word recall, delayed word recall, word recognition, and picture recognition)		continuity of attention versus placebo at 1–2 h after administration.
Kay, 2015	Fesoterodine 4/8mg, alprazolam, placebo	Placebo-controlled, double-blind, double-dummy crossover study	Healthy elderly (65-85 years of age, n=20)	CogState and the Rey Auditory Verbal Learning Test (RAVLT)	1 week (evaluation at the end of the study)	No significant change in any of the cognitive measures compared to placebo.
Geller, 2017	Tropium ER 60mg, placebo	Randomised, double-blinded, placebo-controlled trial	Healthy women (mean age 68, n=45)	Hopkins Verbal Learning Test-Revised, Mini mental status X, digit span, Trails A & B.	4 weeks (evaluation at the end of study)	No change in cognitive function with tropium compared to placebo.
Kosilov, 2018	Solifenacin 20mg + tropium 60mg, Solifenacin 10mg + tropium 30mg, placebo	3 arm randomised clinical trial	Healthy elderly 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 to placebo.

\*MMSE- Mini-mental State Examination

**Table 2. Summary of studies examining overactive bladder anticholinergic use and long-term cognitive decline**

Study	Study design	SettingPopulation	Mean-age, yearsOutcome	Study-duration, monthsEvaluation Period	N prescribed OAB anticholinergics	Results
Esin 2015	Prospective cohort study	Geriatric outpatient clinic in Turkey (mean age 74, 92% women)	74MMSE	6	140	Significant mean decline of 0.4 MMSE points for 50 patients taking darifenacin, but non-significant decline of 0.2 points for 43 oxybutynin initiators, no change for 26 trospium initiators, and 0.1 point increase for 21 tolterodine initiators, compared to 28 patients in the exercise group with no change in MMSE.
Iyer 2019	Prospective cohort study	US urogynecology centre (mean age 77, 100% women)	77MOCA	12	60	Non-significant mean 0.37 point greater decline in MOCA in 59 women prescribed oxybutynin or 1 woman prescribed trospium compared to 46 women in the control group. However, when excluding those with neurological disease, this mean decline in MOCA was only 0.15 points greater in 50 oxybutynin/trospium users compared to the control group.
Moga 2017	Retrospective cohort study	US NACC cohort – participants with normal cognition (mean age 77, 58% women)	77MMSE	12	259	Adjusted odds ratio of 1.26 (95% CI 0.99-1.62) for any decline in MMSE for 259 new OAB anticholinergic users compared to 3,269 non-users. Adjusted odds ratio of 1.42 (95% CI 1.05-1.92) for any decline in MMSE for non-selective agent use compared to no-use.

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Abbreviations: MMSE = Mini-Mental State Examination, MOCA = Montreal Cognitive Assessment, NACC = National Alzheimer's Coordinating Center

**Table 3. Summary of observational studies using administrative data that examine overactive bladder anticholinergic use and dementia incidence**

Study	Study design	Data source	Mean age, years	% Male	Study duration, years	N prescribed OAB anticholinergics	Multivariable regression adjusted results	
Barthold 2020	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. Odds ratio (95% CI) for dementia compared to 1-364 TSDDs of any OAB anticholinergic:	
							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)
Coupland 2019	Subgroup analysis of case-control study	UK primary care database (Qresearch)	76	37%	1-11	25,642	Odds ratio (95% CI) for dementia compared to no prescription:	
							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)							
Liu 2020	Subgroup analysis of retrospective cohort study	Taiwan National Health Insurance Research Data set	64	51%	2-15	4,542	Hazard ratio (95% CI) for dementia of 1.13 (0.93-1.23) for OAB anticholinergic prescription compared to none.	
Richardson 2018	Subgroup analysis of case-control study	UK primary care database (Clinical Practice Research Datalink)	71	37%	4-20	20,134	Odds ratio (95% CI) for dementia of 1.18 (1.13-1.23) for OAB anticholinergic prescription compared to none. Odds ratios (95% CI) by cumulative DDDs compared to no prescription:	
							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)
≥1460 DDDs	1.24 (1.07-1.44)							

Wang 2019	Retrospective cohort study of adults with LUTS	Taiwan National Health Insurance Research Data set	66	84%	1-12	2,731	Hazard ratio (95% CI) for dementia compared to <28 DDDs.	
							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)
Welk 2020	Retrospective cohort study of adults without depression	Health administrative databases from Ontario, Canada	73	56%	0-3	47,324	Hazard ratio (95% CI) for dementia of 1.23 (1.12-1.35) for OAB anticholinergic prescription compared to 23,662 patients prescribed mirabegron.	
Yang 2017	Retrospective cohort study of adults with diabetes	Taiwan National Health Insurance Research Data set	62	64%	0.5-6	7,620	Hazard ratios for dementia compared to 2,540 diabetic non-users matched on age, sex and year:	
							Oxybutynin	2.35 (1.96-2.81)
							Solifenacin	2.16 (1.81-2.58)
							Tolterodine	2.24 (1.85-2.73)

Abbreviations: CI = confidence interval; DDD = Defined Daily Dose; LUTS = Lower urinary tract symptoms; OAB = overactive bladder; TSDD = total standardized daily doses

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