Review Article

The impact of anticholinergics on cognitive function in patients with neurogenic lower urinary tract dysfunction: A narrative review

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ABSTRACT

This narrative review discusses the relationship between anticholinergic medications and cognitive change specifically in patients with neurogenic lower urinary tract dysfunction (NLUTD). NLUTD is prevalent in various conditions, including spinal cord injury (SCI), spina bifida (SB), multiple sclerosis (MS), Parkinson's, stroke, and dementia and often requires anticholinergic overactive bladder (OAB) medications. In the general population, and among those with OAB, several studies have found a significant association between this class of medications and cognitive side effects, mostly when used for > 90 days. These cognitive side effects may be particularly relevant to people with NLUTD due to their higher baseline risk of cognitive impairment. Two studies (one in people with SCI and another in MS) found evidence of cognitive impairment with the use of OAB anticholinergics (specifically oxybutynin and tolterodine). People with dementia commonly use OAB anticholinergics, and there is evidence that oxybutynin and tolterodine may impair cognition in this population. Two recent studies in children with SB studied 12 months of solifenacin and 6 months of fesoterodine/oxybutynin and found there was no significant change in neuropsychological testing. Clinical studies in people with Parkinson's disease and prior stroke have not shown that trospium, darifenacin, or fesoterodine have a significant impact on cognitive measures. In summary, oxybutynin and tolterodine may pose a higher risk of cognitive impairment than newer OAB anticholinergics in people with NLUTD; there is no evidence that children with SB experience cognitive impairment with OAB anticholinergics. Further study is necessary to confirm cognitive safety, particularly as the NLUTD population may have a high exposure to OAB anticholinergics. Advocating for potentially safer OAB medications is necessary if there is concern about cognitive risks.

INTRODUCTION TO NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

Neurogenic lower urinary tract dysfunction (NLUTD) is defined by the International Continence Society as "abnormal or difficult function of the bladder and urethra (and/or prostate in men) in the context of a clinically confirmed relevant neurologic disorder."[1] This occurs across many different neurologic diseases with varying degrees of frequency. For example, after spinal cord injury (SCI, which occurs in 3–10/100,000 people), NLUTD is almost universal, with 90% of traumatic SCI patients having an unfavorable urodynamic finding in the 1st year after their injury.[2] This is similar in spina bifida (SB, which occurs in approximately 30–40/100,000 people) where almost all people have some sort of bladder impairment, and over half have urinary incontinence.[3] Other diseases such as multiple sclerosis (MS, 80–250/100,000 depending on the country) tend to have increased NLUTD symptoms as the disease progresses.[4] Numerous other diseases can be associated with NLUTD, including common ones such as dementia, Parkinson's disease, and stroke,[5] and rare conditions such

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as hereditary spastic paraplegia, Guillain–Barre syndrome, and multisystem atrophy.[6,7]

A common symptom for most NLUTD patients is the presence of urinary urgency and incontinence. These symptoms of NLUTD are analogous to overactive bladder (OAB, which is defined as urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with or without urinary incontinence, in the absence of infection, or other detectable disease).[1] Therefore, the clinical syndrome of OAB is different from similar symptoms in someone with NLUTD only because it is idiopathic nature; when these same OAB symptoms occur in the setting of a neurologic disease, they are usually attributed to changes in the neurologic control of micturition that accompany the disease process. In many cases of neurologic disease, these symptoms can be correlated with neurogenic detrusor overactivity (NDO) on a urodynamic study.

The treatment of symptoms such as urgency and urgency incontinence in both OAB and NLUTD includes initial conservative therapies and then medical therapy. Conservative measures (such as bladder training, reduced fluid/caffeine intake, weight loss, bowel optimization, pelvic floor rehabilitation, and pessaries)[8] are applicable to the general population with OAB and/or stress urinary incontinence. However, these less/noninvasive interventions have not had a high degree of study among the many different neurologic diseases; however some, such as pelvic floor therapy, have been shown in meta-analyses to be effective in people with SCI[9] and MS.[10]

Therefore, due to the nature of their disease and the associated functional limitations, many patients with NLUTD require treatment with medications. The exact proportion of patients with NLUTD that require medical therapy is not known; however, an observational administrative data study from the United Kingdom found that among 3913 people with likely/confirmed NLUTD, 92% received at least one prescription over the year for either an anticholinergic or beta-3 agonist OAB medication.[11] The use of anticholinergic OAB medications is associated with potential side effects in the general population, such as dry mouth, constipation, and dyspepsia.[12] Studies in some NLUTD conditions, such as SCI, have demonstrated that anticholinergics increase rectal compliance and cause constipation.[13] However, it is the evolving literature around cognitive complications arising from anticholinergic medication that is the focus of this narrative review.

ANTICHOLINERGIC OVERACTIVE BLADDER MEDICATIONS AND COGNITIVE CHANGE/ DEMENTIA

Cognitive complications have been associated with anticholinergic medications in general since the 1970s. The mechanism by which they may cause cognitive decline likely involves blocking M1 receptors in the central nervous system; this has been shown to reduce cognitive performance in animal models and human studies, increase protein levels associated with Alzheimer's disease, and cause neuronal cell atrophy and death.[14]

A randomized controlled trial published in European Urology in 2006 brought this to the forefront of urologist's minds. Kay *et al*. randomized health subjects (mean age: 67 years) to 3 weeks of oxybutynin, darifenacin, or placebo.[15] They used the name-face association test to measure delayed recall at the end of the 3 weeks and found that compared to placebo and darifenacin, oxybutynin resulted in a significantly lower score, equivalent to 10 years of brain aging, and participants were not able to self-perceive these changes. Additional high-profile studies have been published in the general medical literature which showed that, in men and women in their 70–80s, the total amount of anticholinergic medication exposure (including drugs used for a variety of conditions) was associated with an increased risk of dementia; most frequently, this was shown with > 90 days of anticholinergic medication exposure.[16,17] A study demonstrated that anticholinergic medication users had increased brain atrophy, poorer cognitive scores, and reduced glucose metabolism in their hippocampus.[18] Systematic reviews have looked at the evidenceon this topic and identified large observational studies including over 600,000 people across 26 studies that evaluated the association between anticholinergic medications and dementia.[19] Keeping in mind that most of the studies had a serious or critical risk of bias, the overall odds ratio for dementia was 1.20 (95% confidence interval [CI] 1.09–1.32) with any use of anticholinergic medications. A Cochrane systematic review on this topic concluded that "there is low-certainty evidence that older adults without cognitive impairment who take medications with anticholinergic effects may be at increased risk of cognitive decline or dementia."[20]

At the same time, the evidence assessing the safety of OAB anticholinergic medications in the general population was evolving. A total of 12 randomized trials evaluated the short-term (<8 weeks) cognitive safety of a variety of OAB anticholinergics (including oxybutynin, tolterodine, solifenacin, fesoterodine, trospium, and darifenacin) have been published.[14] In general, oxybutynin had negative cognitive effects, including evidence that it impaired memory, attention, and reaction times, negatively impacted electroencephalogram readings, and reduced REM sleep quality. However, newer OAB anticholinergics (solifenacin, darifenacin, trospium, and fesoterodine) were generally not significantly different from placebo in measures of cognitive impairment. A systematic review focused on OAB anticholinergic medications found similar results.[21] While this clinical trial data on cognitive impairment are reassuring

for the newer generation OAB anticholinergic medications, the risk of dementia has been shown to be present with OAB anticholinergic medications in general. Data from Ontario, Canada, were used to compare the risk of dementia among similar users of OAB anticholinergics and OAB beta-3 agonist users (mirabegron); this study demonstrated that the risk of dementia was 23% higher among users of OAB anticholinergics.[22] A case–control study from France also demonstrated a dose-dependent increased risk of dementia with the use of OAB anticholinergics (specifically solifenacin and oxybutynin).[23]

COGNITIVE FUNCTION IN PEOPLE LIVING WITH SPINAL CORD INJURY, MULTIPLE SCLEROSIS, AND SPINA BIFIDA

It is important to acknowledge the special cognitive considerations among people living with NLUTD. Some of the conditions (such as dementia) are associated with obvious cognitive changes. However, other commonly studied NLUTD diseases are also associated with an increased risk of cognitive impairment.

People living with SCI have an increased risk of cognitive impairment, independent of the SCI level.[24] Studies have shown that SCI is associated with a 13-fold higher rate of cognitive changes such as decreased attention span, memory, learning, and concentration.[24] People living with SCI are also at an increased risk of dementia, however, it is interesting to note that the published study on this topic did not account for the use of anticholinergic medications, which could be a significant confounder.[25] Functional magnetic resonance imaging studies have shown that cortical networks are reorganized after SCI, and cognitive changes may be the result of different biochemical and neuroinflammatory pathways.

Approximately 2/3 of people with MS have cognitive impairment, most often in the areas of attention, delayed memory, and executive functions.[26] Declining cognition is an important finding, as it is a sign of MS progression and can lead to treatment intensification; conversely, cognitive rehabilitation strategies are an important intervention for people living with MS to try and prevent or slow cognitive changes.[27]

Finally, people living with SB also have evidence of a higher rate of cognitive impairment. They have high self-reported working memory difficulties. Cognitive testing across several studies has documented impaired memory and attention.[28] While one would hypothesize that the presence of an intraventricular shunt, or multiple shunt revisions would be a risk factor for cognitive impairment, the evidence on this topic in a recent systematic review was inconsistent.[28]

In summary, commonly studied populations with NLUTD have baseline risks for cognitive impairment. Intuitively, this would make minimizing the risk of medication-related cognitive side effects an important priority. Relevant to the discussion about OAB anticholinergics, people living with NLUTD have a significantly higher anticholinergic burden as a result of multiple medications; the mean anticholinergic cognitive burden scale score was 6.6 (standard deviation: 5.9) in a UK sample of people with NLUTD,[11] whereas older people who are diagnosed with OAB have an anticholinergic cognitive burden scale score of 2.4 (standard deviation: 1.7).[29]

IS THERE EVIDENCE THAT PEOPLE LIVING WITH SPINAL CORD INJURY, MULTIPLE SCLEROSIS, OR SPINA BIFIDA WHO USE OVERACTIVE BLADDER ANTICHOLINERGIC MEDICATIONS ARE AT INCREASED RISK OF COGNITIVE CHANGE?

There are studies in both adults and children with NLUTD that evaluate cognitive change, however, this population is not as well studied as the general OAB population. There are three small clinical trials evaluating the impact of OAB anticholinergic medications in people living with SCI. Krebs *et al*. studied 29 individuals with an acute SCI (within 8 weeks) who were undergoing urodynamics.[30] There were 19/29 that did not require OAB anticholinergics (controls) and 10 who did require an OAB anticholinergic because of NDO. They excluded people with a coexisting brain injury, psychiatric diagnoses, age > 65 years, and lesions above C5. The OAB anticholinergics included darifenacin, solifenacin, and fesoterodine. At baseline, there were differences between the groups, and after 3 months, the groups had no new significant differences on several cognitive tests, and both groups had percentile rankings for the various tests in the normal range. The study was underpowered because of slow recruitment, and no firm conclusion could be drawn about cognitive impairment other than there was no large degree of impairment evident.

A pilot study switched 20 older (>60 years of age) people with SCI from their chronic OAB anticholinergic medication to mirabegron.[31] After 6 months, participants had significantly improved immediate and delayed recall and executive function, as well as a significant improvement in their urinary symptoms. Importantly, the majority (12/20) were taking oxybutynin or tolterodine before they were switched to mirabegron. Limitations of this study include the pre–post design, which is susceptible to the practice effect (where the patient improves because they have "practiced" the cognitive test once before), and the lack of blinding of patients or assessors.

Finally, a phase II pre–post study evaluated 12 people (mean age: 42) with SCI to see if fesoterodine could reduce autonomic dysreflexia and improve incontinence-related quality of life (QOL).[32] The Montreal Cognitive Assessment (MoCA) test was used to assess overall cognitive function, and it did

not change significantly over the 10–12-week study period. Limitations are like the other pre–post studies, and likely, the MoCA would only detect a fairly substantial cognitive change.

In people living with MS, a propensity-matched cohort study was performed in those starting oxybutynin or tolterodine (mean age: 48).[33] The brief international cognitive assessment for MS tests was given at baseline and 12 weeks later. There were 48 people with MS who started oxybutynin or tolterodine and 21 matched controls. At the end of the study, control patients improved their cognitive function test scores (consistent with a practice effect), whereas the people who started oxybutynin or tolterodine did not improve and had significantly lower scores than the controls.

Finally, the question of the cognitive safety of OAB anticholinergics commonly comes up for pediatric users. These studies are generally done in children with SB given that is the most common etiology of NLUTD in pediatrics. A study of children 6 months to 18 years of age who were treated with solifenacin found that after 1 year, there was no significant decline in four different cognitive tests.[34] However, without a control group, cognitive testing is hard to interpret in children with such a large age range, and this is compounded by significant cognitive development that occurs over the course of a year. A randomized study of 124 children > 25 kg and 57 children ≤ 25 kg found that fesoterodine and oxybutynin did not produce a clinically significant detrimental effect on cognitive function or behavior.[35] A small randomized crossover trial of 14 children (with only one having NLUTD due to SB, and the rest having urinary urgency) found that those that used oxybutynin or tolterodine had no changes to their attention and memory scores on neuropsychological testing.[36]

IS THERE EVIDENCE THAT PEOPLE LIVING WITH DEMENTIA, PARKINSON'S DISEASE, OR CEREBROVASCULAR ACCIDENT WHO USE OVERACTIVE BLADDER ANTICHOLINERGIC MEDICATIONS ARE AT INCREASED RISK OF COGNITIVE CHANGE?

People living with dementia have also been a frequently studied population. This is not surprising given that this is a particularly vulnerable population for cognitive side effects, and the associated degeneration of the brain's frontal lobe predisposes patients to urinary incontinence. A study using Medicare data from 2013 to 2015 found that almost 1/3 of older people (>65 years of age) with dementia also have OAB.[37] Approximately 1/3 of those with both dementia and OAB used an OAB anticholinergic, and most frequently this was oxybutynin. A retrospective cohort study of 540 people with dementia and OAB found that oxybutynin and tolterodine led to a statistically significant decrease in their mini–mental state examination score (by 1.9 points/year), and the decrease in those who were using newer OAB anticholinergics (darifenacin, fesoterodine, trospium, mirabegron, solifenacin) was not statistically significant.[38] A study using the National Alzheimer's Coordinating Center data found that in a group of people with mixed cognitive states (normal, mild impairment, and dementia), those who used oxybutynin or tolterodine had a numerically increased risk of worsening clinical dementia rating score (odds ratio 1.65, 95% CI 0.98–2.77), however, the *P* value was just beyond the traditional cutoff for significance ($P = 0.06$).[39] In the primary analysis (which included all OAB anticholinergics), however, there was no significant difference in the primary or secondary cognitive outcomes.

A few studies have addressed cognitive function with OAB anticholinergic treatment in people with Parkinson's disease or after a cerebrovascular accident (CVA). A randomized placebo-controlled trial enrolled 63 patients with Parkinson's disease and a mean age of 68 years.[40] After 4 weeks of treatment, there was no significant difference in the MMSE score change among those randomized to placebo or fesoterodine 4 mg (–0.4 vs. –0.7, $P = 0.28$). Sixty patients with Parkinson's disease (with a mean age of 56) were treated with trospium or tibial neuromodulation; after 1 year of treatment, the cognitive status (measured with the MoCA) of both groups did not change significantly.[41] A randomized clinical trial of patients who were approximately 8 months post-CVA found no significant change in MoCA scores after 3 months of treatment with either darifenacin 7.5 mg (an OAB anticholinergic) or mirabegron 25 mg (a beta-3 agonist).[42] These results are reassuring and in keeping with literature in the general population on the cognitive risks of these newer OAB anticholinergics, however, while the use of the MMSE/MoCA to measure cognitive change helps to rule out a large cognitive effect, smaller effects could have gone unmeasured.

A study of imidafenacin's effect (a newer OAB anticholinergic that is not widely available) in a group of 62 people with mixed NLUTD (primarily white matter disease, dementia, and Parkinson's disease) found that several cognitive measures did not change significantly after 3 months; however, the lack of a control group means that there may have been suppression of the practice effect (expected improved scores), and no significant change in the scores actually represents a poor cognitive outcome.[43] A multicenter study included 102 people with early dementia, Parkinson's disease, or stroke.[44] They all had symptoms of OAB and detrusor overactivity, and appear to have been randomized to solifenacin, mirabegron, or a combination of the two. There was no statistically significant difference in the MMSE at 3 and 6 months, although interestingly, the groups had a numerically higher score from baseline to 6 months.

CONCLUSIONS

The studies in people with SCI do not provide strong evidence that OAB anticholinergic use causes cognitive impairment. The one study showing a significant association included many oxybutynin and tolterodine users, while the other studies used predominantly newer OAB anticholinergics; this may explain the mixed results. A small, matched-cohort study in people with MS demonstrated significantly worse cognitive scores in new users of oxybutynin or tolterodine compared to the control group. The studies in people with dementia are generally consistent in showing that oxybutynin and tolterodine seem to be more likely to cause cognitive decline, however, some of these results were not statistically significant. In children with SB, two recent studies did not find evidence that 6–12 months of newer OAB anticholinergics (specifically solifenacin and fesoterodine) or oxybutynin caused cognitive impairment.

Based on these studies, it appears that, like the general population, oxybutynin and tolterodine may pose a higher risk than newer OAB anticholinergics in people with NLUTD. This is broadly consistent with the evidence that has come from the OAB population.[14] This may result from the increased lipophilicity, and affinity for M1 receptors that is seen with oxybutynin and tolterodine; conversely, several of the newer OAB anticholinergics take advantage of neurophysiologic mechanisms to reduce accumulation in the brain, such as drug metabolites that are substrates of active transporters, have a larger size, and or have an increased polarity.[14]

It is concerning that vulnerable populations, such as those with existing cognitive impairment/dementia, are still using oxybutynin. Data from the United States have shown that the proportion of people with cognitive impairment/dementia who start oxybutynin has increased from 24% in 2008 to 41% in 2011 (likely due to cost and insurance restrictions).[45] It will be important that neurourologists and others that treat NLUTD continue to advocate that patients have access to newer anticholinergics or beta-3 agonists when necessary. A large, randomized clinical trial among people with NLUTD due to MS and SCI demonstrated solifenacin was effective at improving urodynamic parameters and patient QOL, and therefore, it may be an acceptable alternative to oxybutynin.[46] In addition, the evolving evidence on mirabegron in NLUTD means this class of medication (beta-3 agonists) may provide a medical option that does not have known cognitive effects.[47]

Further study is necessary to confirm the cognitive safety of OAB anticholinergics, particularly as the NLUTD population may have a high exposure to these medications. Future research should include a longer duration of exposure, a comparison group, and should employ condition-appropriate, sensitive tests of attention, memory, and executive function.

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