

Clinical Consensus Statement: Association of Anticholinergic Medication Use and Cognition in Women With Overactive Bladder

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Abstract: Overactive bladder affects a significant portion of the overall population and has substantial impact on daily activities and quality of life. First-line treatment of overactive bladder includes behavioral therapies, which may be combined with pharmacologic management as indicated. Anticholinergic medications and β -3 agonists are often used as initial pharmacologic therapy, but caution should be taken in prescribing anticholinergic medications in frail or cognitively impaired patients. Recently, additional concerns have emerged regarding prolonged use of anticholinergic medications and the associated risk of cognitive impairment, dementia, and Alzheimer disease in the general population. Given the available evidence, which has shown significant associations between anticholinergic medication use and increased risk of cognitive impairment and dementia, providers should counsel on the associated risks, prescribe the lowest effective dose, and consider alternative medications in patients at risk.

Key Words: overactive bladder, anticholinergic, antimuscarinic, cognitive impairment, dementia

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Overactive bladder (OAB) is a clinical diagnosis characterized by urinary urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia with urinary incontinence (OAB-wet) or without (OAB-dry) in the absence of urinary tract infection or other detectable disease. The overall prevalence of OAB in the general population is as high as 12% to 17%, and it significantly impacts the quality of life of affected individuals.^{1–5} The underlying pathophysiology of OAB is detrusor overactivity (DO), a urodynamic diagnosis defined by involuntary detrusor contraction during filling cystometrograms.⁶

In patients desiring treatment for symptoms of OAB/DO, behavioral therapies, including fluid management, bladder training, urge suppression, and pelvic floor muscle strengthening, should be instituted first. If behavioral therapies do not control symptoms, then the American Urological Association and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction Guideline on OAB recommends antimuscarinic or β -3 agonists as pharmacologic treatment.⁷ Trials of different medications in these classes in varying doses are acceptable; however, extended-release formulations are preferred because of lower rates of dry mouth. The guideline does note that clinicians should use caution in prescribing antimuscarinic or β -3 agonists for OAB

in frail patients or those with cognitive deficits. The American Urogynecologic Society's "Choose Wisely" campaign recommends the avoidance of anticholinergic medications to treat OAB in women older than 70 years.⁸

Antimuscarinic medications are a type of anticholinergic medication that block the activity of acetylcholine at muscarinic receptors. Muscarinic receptors are distributed throughout the body and give rise to the potential for a broad range of anticholinergic adverse effects such as dry mouth, blurred vision, constipation, and impaired cognition.⁹ Oxybutynin and tolterodine, the most studied medications, were compared in a Cochrane review.¹⁰ Although these medications did not statistically differ in quality of life and subjective or objective outcomes, there were significantly fewer study withdrawals because of adverse events and less risk of dry mouth with tolterodine. In older patients, mirabegron, a β -3 agonist, has been shown to have a more favorable tolerability profile in comparison with antimuscarinics.¹¹ Over time, the properties of anticholinergic medications have been modified in an attempt to mitigate undesirable cognitive adverse effects by improving muscarinic receptor selectivity and decreasing its ability to cross the blood-brain barrier. In a nonclinical study, 5-hydroxymethyl tolterodine, darifenacin, and trospium displayed low brain penetration, whereas oxybutynin, solifenacin, and tolterodine showed significant brain penetration.¹²

Several publications have raised concerns about anticholinergic medications in general and the associated risk of cognitive impairment, dementia, and Alzheimer disease.^{13–19} A population-based prospective cohort study of 3434 participants sampled from an integrated health care delivery system examined the association between cumulative anticholinergic use and the risk of dementia.¹³ Bladder antimuscarinics accounted for 10.5% of anticholinergic medication use. In comparison, antidepressant medications comprised 63.1%, and antihistamines comprised 17.2%. Participants in the highest exposure category—corresponding to oxybutynin chloride 5 mg taken daily for more than 3 years—had a significantly increased risk of dementia (adjusted hazard ratio [HR], 1.54; 95% confidence interval, 1.21–1.96) or Alzheimer disease (adjusted HR, 1.63; 95% confidence interval, 1.24–2.14) compared with those with no use. Although the study design supports only an association with no ability to assume causality, the relationship is compelling. A notable strength of the study was that the authors took measures to correct for bias because of the use of other anticholinergic medications to treat the prodromal symptoms of dementia (eg, antidepressant medications used to treat depression-like symptoms secondary to undiagnosed early dementia).

Another study examined the association between anticholinergic medication use and neuroimaging biomarkers of brain

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metabolism and atrophy in a cohort of participants from 2 longitudinal studies, providing a biologic basis to the findings in previous studies.¹⁴ Significant differences in memory and executive function were noted in measures of cognitive performance when comparing anticholinergic users and nonusers. In addition, anticholinergic users showed significantly reduced brain glucose metabolism and evidence of temporal lobe and whole-brain atrophy compared with nonusers. Anticholinergic medication use was also associated with progression to mild cognitive impairment and/or Alzheimer disease ($P = 0.01$; HR, 2.47). This risk was greatest in patients taking drugs with the highest anticholinergic activity.

A more recent population-based, retrospective, matched cohort study evaluated the risk of dementia in 47,324 new users of anticholinergic medications compared with 23,662 new users of a β -3 receptor agonist for the treatment of OAB. The authors reported an increased risk of dementia among anticholinergic users compared with β -3 agonist users (HR, 1.23, 95% CI, 1.12–1.35). Although these findings support the association between anticholinergic use and dementia, the differences in rates of dementia between groups were relatively small and the study was limited by its retrospective nature. In addition, the effect size was unequal between men and women, with no statistically significant difference seen among women during subgroup analysis.²⁰

When considering these studies, several limitations deserve mention. First, there is no single standard method used to estimate total anticholinergic burden from all sources including antidepressants, antihistamines, bladder antimuscarinics, and other medications; therefore, overall anticholinergic exposure and outcomes are not easily compared. Multiple risk scales are available for estimating anticholinergic burden of medications.^{21,22} In addition, the methods of collecting medication use, although more reliable with the use of electronic pharmacy dispensing data, may not accurately reflect actual use. Most of the available studies on effect of anticholinergic medications on cognitive function do not make distinction on their capacity to cross the blood-brain barrier. Although some anticholinergic medications seem less likely to cross the blood-brain barrier, there are insufficient clinical data to demonstrate safety with regard to cognitive concerns. Furthermore, there may be unobserved confounding or bias inherent to these observational studies. Despite these limitations, the literature presents data supporting the association between anticholinergic medication use and cognitive impairment, dementia, and Alzheimer disease.

Recommendations:

- When behavioral therapies fail and pharmacologic treatment of OAB/DO is considered, providers should counsel on the associated risk of cognitive impairment, dementia, and Alzheimer disease associated with anticholinergic medications in comparison with the potential benefits related to improvement in quality of life or overall health of the individual patient.
- To reduce overall anticholinergic burden, the lowest effective dose should be prescribed, and consideration should be given to alternative medications such as β -3 agonists.
- Consideration should be given to changing or decreasing the dosage of other anticholinergic medications that a patient may be taking.
- As recommended by the American Urogynecologic Society's "Choosing Wisely" campaign, use of anticholinergic medications to treat OAB in women older than 70 years should be avoided.
- When anticholinergic medications have to be used in elderly patients, consideration should be given to use those that have low potential to cross the blood-brain barrier, recognizing that there are limited clinical data.
- Third-line therapies such as intradetrusor onabotulinum toxin A or neuromodulation should also be considered in patients not desiring to use medications for OAB/DO because of their adverse effects.

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This document reflects clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Its content is not intended to be a substitute for professional medical judgment, diagnosis, or treatment. The ultimate judgment regarding any specific procedure or treatment is to be made by the physician and patient in light of all circumstances presented by the patient.

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