



Platinum Opinion

Anticholinergic Burden in the Elderly Population: An Emerging Concern

Hudson Pierce, Dominique Thomas, Tirsit Asfaw, Bilal Chughtai *

Department of Urology, Weill Cornell Medicine, New York, NY, USA

Antimuscarinic medications are routinely prescribed for older adults, particularly as first-line pharmacological treatment for controlling symptoms of overactive bladder (OAB). However, increased anticholinergic burden (AB) has been associated with adverse outcomes in the elderly population, and emerging research suggests that anticholinergic use in these patients can have irreversible cognitive effects. We advocate for standardization of anticholinergic risk assessment, as well as improved provider education regarding AB and the promotion of optimal prescribing practices in the treatment of OAB in the elderly.

OAB is a symptom complex characterized by urinary urgency with or without urinary incontinence, typically accompanied by frequency and nocturia. The prevalence of OAB increases with age in both sexes, and can have a significant impact on quality of life and daily functioning [1]. The first-line therapies for OAB include conservative interventions such as fluid restrictions and behavioral modifications. However, older persons are more likely to seek medical therapy, and antimuscarinics result in greater symptomatic improvement compared to behavioral modifications alone [1].

Antimuscarinics improve symptoms of detrusor overactivity by inhibiting the binding of acetylcholine to the M2 and M3 receptors within the bladder. Peripheral side effects include dry mouth, constipation, and blurred vision, and adverse central nervous system (CNS) effects include confusion, sedation, and dizziness. Recent research has further suggested an association between higher cumulative anticholinergic use and the risk of Alzheimer disease and dementia [2,3]. The evidence must be considered in the context of study limitations, including their observational nature, lack of standardization for AB measurement, and molecular differences between the antimuscarinics studied.

However, the potential risk of irreversible cognitive effects suggests that AB should be considered an emerging issue, particularly in regard to elderly patients.

Multimorbidity and polypharmacy in the elderly population raise the probability of exposure to anticholinergic drugs. The elderly are also more susceptible to adverse effects from anticholinergic action because of a constellation of age-related physiological changes that influence pharmacodynamics and pharmacokinetics. The blood-brain barrier typically becomes increasingly permeable with age, and increasing age has also been associated with a decline in cholinergic neurotransmission in the CNS, which theoretically may compound antimuscarinic antagonism and increase susceptibility to adverse effects [4]. Older patients may also have impairments in hepatic metabolism, renal clearance, or volume distribution that could collectively increase toxicity.

Anticholinergic risk-assessment scales quantify AB for research and clinical purposes. At least 18 scales have been developed, with varying degrees of validation regarding association between scores and adverse outcomes [5]. However, there is no consensus on which scale is optimal, and there is significant variability between scales regarding drug inclusion and the anticholinergic action of each drug. Most scales assign agents a score of 0–3 in order of increasing anticholinergic action, and scores are then summed linearly to produce a measure of cumulative AB, but this method downplays complicated drug-drug interactions and dose-dependent effects. Ideally, an assessment tool would incorporate the pharmacodynamics and pharmacokinetics of the anticholinergic drugs, including muscarinic receptor-subtype specificity, dosage, clearance, and elimination. A pilot study by Xu et al. [6] showed promise in deriving a computational model for anticholinergic toxicity

* Corresponding author. Department of Urology, Weill Cornell Medicine, 425 East 61st Street, New York, NY 10065, USA. Tel. +1 646 9624811; Fax: +1 646 9620140.
E-mail address: bic9008@med.cornell.edu (B. Chughtai).



from big pharmacological and healthcare data. Much further research is required, but this is a step in the right direction and could help in addressing many of the weaknesses of current scales.

Evidence regarding cognitive effects of individual antimuscarinics is also not uniform. Available agents differ in regard to propensity for binding to bladder-specific muscarinic receptor subtypes and for penetration into the CNS. Oral oxybutynin has been associated with cognitive impairment in the elderly in the short term, and along with tolterodine has been associated with a higher risk of incident dementia [2]. By contrast, short-term studies in older adults have demonstrated little to no cognitive impairment associated with fesoterodine, solifenacin, or trosipium [7–9]. Trosipium is a quaternary ammine and it has been shown that it was absent in the cerebrospinal fluid of study participants, so theoretically it has less potential for CNS penetration [9]. Mirabegron, a β_3 -adrenoceptor agonist, is a newer alternative agent effective in treating symptoms of OAB, but there are no long-term studies regarding its effect on cognitive function. More longitudinal research is urgently needed to fully characterize the effect of both bladder antimuscarinics and β_3 -adrenoceptor agonists on cognition.

In the clinical sphere, better provider education is also necessary. In a survey of providers treating OAB, including urologists and urogynecologists, Araklitis et al. [10] found deficiencies in areas such as knowledge of the potential harmful cognitive effects of anticholinergics, understanding of the mechanisms of action of individual antimuscarinics, and ability to assess AB. Even for educated clinicians, however, attempts to exercise optimal prescribing practices can be difficult. Insurance requirements and clinical guidelines may leave a provider with little choice other than prescription of certain antimuscarinics. Meaningfully decreasing anticholinergic exposure may be implausible in short visits with medically complicated patients, especially in the absence of a standardized AB assessment tool.

Our aim is to draw attention to AB in the elderly as a critical topic for consideration by urologists. There are limitations to the current evidence supporting an association between antimuscarinic use and dementia, and much further research into the long-term cognitive effects of antimuscarinics is needed, particularly for those that have been associated with fewer adverse CNS effects in the short term. The development of an anticholinergic risk assessment tool that encompasses the full complexity of anticholinergic medications would help to guide these efforts. Antimuscarinics can also have a significant positive impact on quality of life in older patients, and their benefits should not be discounted in the meantime. However, clinicians should recognize the potential of antimuscarinics

for long-term cognitive impairment, especially in populations such as the frail elderly and those at higher risk of dementia at baseline, and perform a risk-benefit analysis for each individual patient. Consideration should be given to selective antimuscarinics with less propensity for CNS penetration, and the lowest effective dose should be prescribed.

Treatment of OAB in the elderly is a delicate balancing act between improving quality of life and AB. It is our responsibility as providers to make every effort to reduce anticholinergic use by older adults, and to address this emerging concern.

Conflicts of interest: Bilal Chughtai is an investigator for Ipsen, Astellas, and Medi-tate, is a key opinion leader for Boston Scientific, and is a current speaker for Allergan and a previous speaker for Mist Pharmaceuticals. The remaining authors have nothing to disclose.

References

- [1] Wagg A. Treating overactive bladder in the elderly. *Can Urol Assoc J* 2011;5(Suppl. 2):S149–51.
- [2] Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ* 2018;361:k1315.
- [3] Risacher SL, McDonald BC, Tallman EF, et al. Association between anticholinergic medication use and cognition, brain metabolism, and brain atrophy in cognitively normal older adults. *JAMA Neurol* 2016;73:721–32.
- [4] Kersten H, Wyller TB. Anticholinergic drug burden in older people's brain—how well is it measured? *Basic Clin Pharmacol Toxicol* 2014;114:151–9.
- [5] Welsh TJ, van der Wardt V, Ojo G, Gordon AL, Gladman JRF. Anticholinergic drug burden tools/scales and adverse outcomes in different clinical settings: a systematic review of reviews. *Drugs Aging* 2018;35:523–38.
- [6] Xu D, Anderson HD, Tao A, et al. Assessing and predicting drug-induced anticholinergic risks: an integrated computational approach. *Ther Adv Drug Saf* 2017;8:361–70.
- [7] Wagg A, Arumi D, Herschorn S, et al. A pooled analysis of the efficacy of fesoterodine for the treatment of overactive bladder, and the relationship between safety, co-morbidity and polypharmacy in patients aged 65 years or older. *Age Ageing* 2017;46:620–6.
- [8] Wagg A, Dale M, Tretter R, Stow B, Compion G. Randomised, multi-centre, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. *Eur Urol* 2013;64:74–81.
- [9] Staskin D, Kay G, Tannenbaum C, et al. Trosipium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. *Int J Clin Pract* 2010;64:1294–300.
- [10] Araklitis G, Thiagamorthy G, Hunter J, Rantell A, Robinson D, Cardozo L. Anticholinergic prescription: are healthcare professionals the real burden? *Int Urogynecol J* 2017;28:1249–56.