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Anticholinergic therapy: A case-based approach

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ABSTRACT

Anticholinergic medication remains integral in the management of women with Overactive Bladder syndrome although there is increasing evidence to support a link with the impairment of cognitive function. This editorial will review the available evidence and discuss the management of patients in order to minimise anticholinergic burden with a particular focus on the elderly.

Anticholinergic medication is commonly used within all branches of clinical practice and over 600 drugs are known to have anticholinergic properties [1], many of which are available as over-the-counter medications [2]. With ageing, the likelihood of exposure to anticholinergic medication increases and polypharmacy is a particular problem in the elderly, with up to 50% of patients prescribed at least one anticholinergic drug. In addition, many elderly women complaining of lower urinary tract symptoms may be prescribed anticholinergic medication for overactive bladder (OAB) syndrome, although the longer-term implications of this anticholinergic burden remain poorly understood by many clinicians in both primary and secondary care [3].

1. What is Anticholinergic Burden – And Does it Matter?

Anticholinergic burden is defined as the cumulative effect of taking one or more drugs that are capable of developing anticholinergic adverse effects and the load increases with the number of medications prescribed [1].

In a two-year longitudinal study of 13,004 participants over the age of 65 years the use of drugs with an anticholinergic effect was associated with a 0.33-point decline in score on the Mini Mental State Examination (MMSE) (95%CI: 0.03–0.64; $p = .03$) and an increased risk in terms of 2-year mortality (OR = 1.68; 95%CI: 1.30–2.16; $p < .001$) [4]. These findings are supported by a systematic review of 46 studies including 60,944 participants that demonstrated a significant decline in cognitive ability with increasing anticholinergic load in addition to an increasing, but non-significant, trend in terms of mortality [5].

The evidence would therefore suggest that anticholinergic drugs should be used with caution, particularly in the elderly, and further evidence is provided by a prospective cohort study of 3434 participants from North America investigating the association of total standardised daily dose (TSDD) of anticholinergic and the onset of dementia and Alzheimer's disease. Overall, a 10-year dose–response relationship was observed for both dementia and Alzheimer's disease (test for trend $p < .001$), with the greatest risk being associated with the highest anticholinergic dose (adjusted hazard ratio 1.54, 95%CI 1.21–1.96) [6]. The impact on cognitive function is thought to be due to the effects on the central nervous system (CNS) of the passage of anticholinergic drugs across the blood–rain barrier (BBB).

2. What is the Blood–Brain Barrier?

The BBB is made up of endothelial cells lining cerebral capillaries [7] and permeability increases with ageing due to epithelial cell shrinkage and the opening of tight junctions [8]. This may occur because of normal ageing, trauma, diabetes, multiple sclerosis, stroke, hypertension, Parkinson's disease and dementia [9]. Small molecules (<400 kDa) which have a neutral charge and which are lipophilic and hydrophobic are more likely to cross the BBB. In addition, the brain has an efflux transport system, permeability-glycoprotein (P-gp), that pumps molecules out of the CNS and therefore reduces levels within the brain. An anticholinergic drug, which is less likely to cross the BBB or is actively pumped out, is therefore less likely to cause CNS side effects [10].

3. Should Anticholinergic Drugs be used in the Elderly?

Whilst the use of antimuscarinic medication is not contraindicated in the elderly, it is important before treating OAB to be aware of *co*-morbidities and also the risk of polypharmacy. Given that many medications may have an anticholinergic effect, it is important to be aware of this prior to initiating therapy in order to reduce the overall

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anticholinergic load. This may be assessed clinically using an anticholinergic burden scale and there are now several validated measures available [10]. In general, the higher the score, the greater the anticholinergic burden, and therefore the greater the risk of cognitive impairment.

4. How do We Choose the Right Drug?

Drugs such as oxybutynin, darifenacin, fesoterodine, solifenacin and tolterodine are tertiary amines, meaning they are more likely to cross the BBB, whilst trospium chloride, being a quaternary amine with lower lipophilicity, is less likely to do so [10].

In addition, trospium, fesoterodine and darifenacin are substrates for P-gp, meaning they are actively pumped out of the CNS and brain/plasma ratios used to assess CNS levels of the drug have been shown to be highest for oxybutynin, intermediate for tolterodine and solifenacin and low for darifenacin, fesoterodine and trospium chloride [10].

Should anticholinergic burden be high, and non-modifiable, then an alternative therapeutic approach may be helpful, by using either a transdermal oxybutynin or a β_3 agonist such as mirabegron.

5. Conclusion

Emerging evidence would appear to suggest an association between the use of anticholinergic medication and the risk of long-term cognitive dysfunction, with the elderly representing a particularly high-risk population. Assessing anticholinergic burden prior to treating OAB should allow a tailored approach using anticholinergic medications which are less likely to cross the BBB or by using an alternative approach such as a transdermal preparation or a β_3 agonist. A better understanding of the relationship between anticholinergic medication and cognitive function should improve patient outcomes, particularly in the elderly.

Contributors

The two authors had equal input into the writing of this editorial.

Conflict of Interest

Dudley Robinson has undertaken consultancy for Astellas, Allergan, Ixaltis, Femeda and Ferring, and done research work for Ixaltis.

George Araklitis has no conflict of interest to declare.

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