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COMMENTARY

Anticholinergic drugs and risk of dementia: Time for action?

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Abstract

Evidence suggests that the prescription of bladder anticholinergics is increasing. Recent studies have accentuated concerns about whether certain prescribed medications could increase risk of dementia, including anticholinergic drugs, and specifically anticholinergics used for bladder symptoms. Nevertheless, it can be difficult to draw together the evidence to review the case for possible causation. Recognising this issue in 1965, Bradford-Hill set out nine criteria to help assess whether evidence of a causal relationship could be inferred between a presumed cause and an observed effect. In this commentary, we explore the extent to which associations between anticholinergics and dementia satisfy the Bradford-Hill criteria and examine the potential implications. First, we look at studies that have examined the relationship between anticholinergic drugs with urological properties (bladder drugs) and the onset of dementia, and then present those studies which specifically focus on the cognitive effects of bladder drugs that affect muscarinic receptors in the brain versus the bladder on older people along with suggestions for future research. We also discuss the risks and benefits of these drugs for treating overactive bladder. If it can be shown that certain medications carry a specific risk of dementia, it is possible that initiatives to change prescribing could become a key tool in reducing the risk of dementia and may be easier to implement than some lifestyle changes.

KEYWORDS
anticholinergics, bladder symptoms, Bradford-Hill criteria, dementia, deprescribing

Anticholinergic drugs have long played an important role in the management of bladder symptoms, which reduce incontinence and urgency[1] while improving quality of life. However, these benefits need to be considered in relation to potential adverse effects. In particular, there is now a need to review the evidence for anticholinergics as a risk factor for the development of dementia. This article focuses on anticholinergics used for bladder symptoms as these are commonly used, particularly in the elderly, and alternative treatments are available.

Several anticholinergic drugs are licensed for treatment of bladder conditions, including selective antimuscarinic drugs that only affect the bladder, such as solifenacin and darifenacin, and nonselective antimuscarinics that affect receptors in both the bladder and the brain, such as oxybutynin. Other bladder treatments without anticholinergic properties include the newer drug mirabegron and non-drug interventions. The trends in defined daily doses (DDDs) of anticholinergics and mirabegron using data from the NHS Business Services Authority on medications dispensed in the community in England between 2010 and 2019 are shown in Figure 1.

In 2019, over 187 million DDDs of these anticholinergics were dispensed, an increase of 61% since 2010. During this period, DDDs

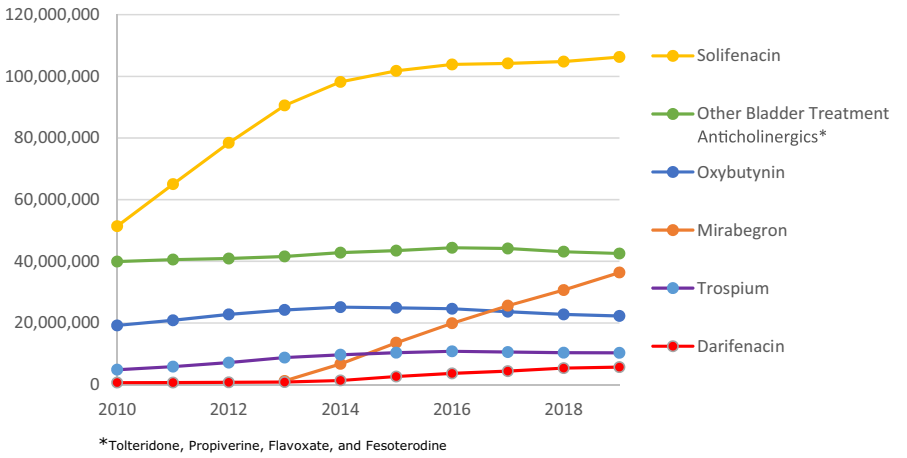

FIGURE 1 Defined daily doses by year of various bladder treatment drugs (2010–2019).

dispensed for solifenacin more than doubled to 106 million in 2019, while DDDs dispensed for oxybutynin increased by 16% to 22 million in 2019, and 36 million DDDs were dispensed for mirabegron in 2019. Given the substantial and increasing prescription of bladder treatment anticholinergics, it is important to have more clarity regarding risks of dementia. To explore a potential causative link between bladder anticholinergics and dementia, we have assessed the evidence using the Bradford Hill[2] criteria, which are listed in Box 1.

Turning to the literature, a growing number of studies, including those by Richardson[3] and Coupland[4] have found a strong longitudinal association between anticholinergic drugs with urological properties and dementia risk over various time intervals between taking the anticholinergic and the development of dementia. Importantly, both studies accounted for protopathic biases by excluding prescriptions in periods close to the diagnosis of dementia. Furthermore, in Coupland's[4] study, the adjusted odds ratios for dementia diagnosis increased with higher cumulative dosages of bladder antimuscarinics, which means that (1) strength of association, (4) temporality, and a (5) biological gradient or dose–response relationship were demonstrated.

Randomized controlled trials (RCTs) investigating anticholinergic drugs with different effects on muscarinic receptors in the brain versus the bladder found that cognitive functions were not compromised by darifenacin (a selective antimuscarinic) but were negatively affected by oxybutynin (a nonselective antimuscarinic).[5] Furthermore, higher doses of oxybutynin were associated with greater memory problems.[5] Trospium[5] and solifenacin[6] (bladder-selective antimuscarinics) were also not associated with cognitive impairment, including higher dosages of solifenacin.[6] Most of these studies involved participants aged 60 years and older. Using the Bradford Hill[2] criteria, these RCTs appear to show (2) consistency, (3) specificity, in that cognitive functions were not compromised by selective antimuscarinics that affect only the bladder, a (5) dose–response relationship, and (8) experimental evidence. It should be noted, however, that while the trials involving darifenacin, solifenacin, and trospium are reassuring,[5,6] the studies were of short duration and assessed cognitive function rather than the development of dementia.

The criteria of plausibility (6), in which the association can be accommodated within existing biological models and coherence (7), which means that the data should not conflict with known biological facts, are supported by the fact that oxybutynin is a small molecule relative to selective antimuscarinics, which increases the ability of this drug to cross the blood–brain barrier. In contrast, trospium, due to its quaternary structure, is much less likely to cross the blood–brain barrier.[7] Furthermore, efflux transporters

BOX 1 Bradford Hill[2] criteria

1) Strength of association, in which the larger the association, the more likely a causal relationship can be inferred.
2) Consistency, or repetitiveness in the findings, where a variety of locations, methods, and populations show the same results.
3) Specificity, in which one exposure causes only one disease.
4) Temporality, in which exposure precedes the disease in time, which can include low exposure over long time periods.
5) Biological gradient, where there is a dose–response relationship between the exposure and the effect.
6) Plausibility, in which the association can be accommodated within existing biological or social models.
7) Coherence, where the cause and effect relationship is bolstered by all of the evidence available to the researcher.
8) Experiment, in which an intervention reduces exposure, thereby reducing the risk of the disease.
9) Analogy, which allows the researcher to accept weaker evidence for a relationship if a stronger causal relationship has been established between a similar agent and a similar disease.

pump darifenacin and trospium from the blood vessels of the cerebral cortex, but no such mechanism has been identified for oxybutynin.[8] Pagoria[8] noted that the blood–brain barrier may be compromised in older people, which may further increase the risk. More generally, anticholinergics may alter the brain resulting in atrophy and reduced glucose metabolism.[9] Risacher[10] found that those who used anticholinergics not only showed cognitive decline on memory tests, but also greater brain atrophy as measured by structural magnetic resonance imaging (MRI) and lower levels of glucose metabolism as measured by positron emission tomography. This supports the premise that the use of anticholinergics alters the cholinergic connections responsible for cognition in older adults. Finally, Perry[11] reported that long-term use of antimuscarinics, in contrast to short-term use, was associated with more neurofibrillary tangles and amyloid plaques, and concluded that the blockade of M_1 receptors may be responsible for this effect. This supports the Bradford Hill[2] criteria of analogy (9) because plaques and tangles are strongly associated with Alzheimer's disease, and the use of antimuscarinics is associated with more plaques and tangles; therefore, antimuscarinics may increase the risk of Alzheimer's disease. It should be noted that only antimuscarinics that block M_1 receptors appear to produce this effect, so bladder drugs, such as darifenacin and solifenacin, which selectively block M_3 receptors,[12,13] may not be linked to Alzheimer's disease.

In summary, it appears that the use of oxybutynin satisfies the Bradford Hill criteria for establishing a causal link with the development of dementia, and this may also be the case for other anticholinergics that easily cross the blood–brain barrier. Should doctors and pharmacists make the case for avoiding anticholinergics associated with risk of dementia? The precautionary principle would suggest that we should act now and advise colleagues not to use anticholinergics associated with dementia for bladder symptoms when there are alternatives that appear to be safer. Anticholinergic burden scales, which assess the cumulative effect of taking medicines with anticholinergic properties, can be used to help clinicians identify patients at risk from the adverse effects of anticholinergic drugs that are linked to dementia. A key challenge is to flag up at-risk patients to clinicians, and this is where GP computer systems can be very helpful due to automation of patient records.

There are, of course, other considerations when balancing benefits and risks when considering prescribing antimuscarinics for bladder symptoms. Antimuscarinic drugs are beneficial in improving the symptoms of overactive bladder, improving quality of life, and reducing incontinence, micturition frequency, and urgency episodes.[14] However, in addition to the risks of dementia associated with oxybutynin, this drug exhibited side effects more commonly than solifenacin or trospium, namely, a greater risk of dry mouth and withdrawals due to adverse effects.[15] Furthermore, although higher doses of oxybutynin and solifenacin were better at controlling bladder symptoms, this was associated with more withdrawals due to adverse effects for oxybutynin and more instances of dry mouth for solifenacin.[15] Mirabegron is a newer drug for controlling bladder symptoms that is not an anticholinergic and is not thought to be associated with dementia; it appears to have fewer side effects than solifenacin but may be less effective in controlling symptoms.[16,17]

Campbell[18] suggests that future research should implement a deprescribing intervention as the next step, to not only investigate whether reducing anticholinergic use improves cholinergic transmission and reduces risk of dementia but also to evaluate the possible harm that comes from deprescribing these drugs. Further research could look at whether substituting selective antimuscarinics or other drugs, such as mirabegron, for nonselective ones improves memory function and delays the onset of dementia in older adults. Of course, as Campbell[18] notes, if deprescribing comes too late in the disease process, then an improvement in cognition may not be detected, so selecting the appropriate population becomes critical in order to maximize the potential of detecting a clinically meaningful change in cognition. The interaction of dementia drugs (acetylcholinesterase inhibitors) and bladder drugs (anticholinergics) also needs to be investigated further as use of anticholinergics may reduce the efficacy of drugs prescribed for treating dementia. If it can be established that certain medications carry a specific increased risk of dementia, it is possible that initiatives to change prescribing could become a key tool in reducing the risk of dementia and may be easier to implement than some lifestyle changes.

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