Managing drugs with anticholinergic activity

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Abstract
Over the past two decades, considerable data have emerged on an association between drugs with anticholinergic activity and serious adverse effects in older people. Well-recognised anticholinergic adverse effects include dry mouth, blurred vision, constipation and urinary retention. Of particular concern is the potential impact on cognitive function with several studies showing that long-term use of medicines with anticholinergic activity is associated with worsening of cognitive function, increased incidence of dementia and increased mortality. This article gives an overview of the evidence, discusses some of the tools used to identify high-risk drugs and highlights issues to consider when prescribing drugs with anticholinergic activity with a view to reducing potential risks in older people and those at highest risk of cognitive impairment.

Key learning points
- Many drugs including some antidepressants, antipsychotics, drugs for Parkinson’s disease, antiepileptic drugs and drugs used in urinary conditions have anticholinergic activity.
- Long-term use of drugs with anticholinergic activity is associated with an increased risk of cognitive decline, dementia and mortality in older people.
- Anticholinergic burden scales can be used to identify high risk drugs.
- The anticholinergic burden of drugs should be considered when initiating drugs in older people and the total anticholinergic burden should be assessed at every medication review or when there are concerns over cognitive function.

Background
Dementia affects 55 million people worldwide, and as the proportion of older people in the population is increasing in nearly every country, this number is expected to continue to rise to 78 million in 2030 and 139 million in 2050.1 There is still no cure for dementia and licensed dementia medications have limited efficacy and are primarily targeted at Alzheimer’s disease. Despite new research focusing on other mechanisms, acetylcholine remains the main neurotransmitter associated with dementia and current treatments act to increase its availability in the brain. Hence, there are concerns that drugs that block or reduce acetylcholine activity in the brain may impair memory and cognitive function.

Over the last 20 years, data have emerged on an association between drugs with anticholinergic activity and serious adverse effects in older people, including worsening of cognitive function, increased incidence of dementia and mortality.2–5 Several large studies have found that the use of drugs with strong anticholinergic activity including some antidepressants, drugs used for urinary frequency, urgency and incontinence, some drugs used to treat Parkinson’s disease and some antiepileptic drugs are associated with an increased risk of dementia in older people.2,3

Drugs with anticholinergic activity are widely prescribed in older people. Survey data from England in over 7500 people aged ≥65 years collected from 1990 to 1993 and 2008 to 2011 showed that use of drugs with potent anticholinergic effects increased from 5.7% of those surveyed to 9.9%.4 The prevalence of drugs with any anticholinergic activity increased from 50% to 64%. This highlights the importance of prescribing these medicines with caution in older people and those at high risk of cognitive impairment, and that alternative treatments should be considered where possible. Limitations of the evidence linking medicines with anticholinergic activity to cognitive decline include the potential for confounding by indication; it is known, for example, that depression can be an early symptom of dementia and Parkinson’s disease is a risk factor for dementia. Moreover, data are from observational studies of relatively short duration that tended to recruit people with fewer comorbidities.6 Nevertheless, while other risk factors for cognitive decline should be addressed (eg, cardiovascular risk factors, hearing impairment, untreated depression, social isolation and physical inactivity), the authors of a systematic review on anticholinergic drugs and the risk of dementia (14 studies, 1 564 181 participants) suggest that drugs with anticholinergic activity are a potential modifiable risk factor for dementia.9–10

Drugs and anticholinergic activity
Drugs that possess anticholinergic activity block the action of acetylcholine at muscarinic receptors and impair cholinergic function in the central and peripheral nervous system. Some drugs exert their main therapeutic effect through anticholinergic activity (eg, hyoscine, oxybutynin, procyclidine), while for other drugs anticholinergic activity is secondary to their main therapeutic action (eg, tricyclic antidepressants, clozapine, some antihistamines). Anticholinergic activity causes well-known peripheral effects (eg, dry mouth, blurred vision, urinary retention, constipation) and central effects including confusion, disorientation, memory impairment, hallucinations and delirium.11–13 In addition, anticholinergic drugs with central action directly
oppose the action of acetylcholinesterase inhibitors used in dementia, thus potentially reducing their clinical efficacy when used concomitantly.9 Although it is not yet known whether drugs with central anticholinergic activity are more harmful than those that act peripherally and do not penetrate the brain, it seems likely to be the case as centrally acting drugs also tend to have peripheral effects. A study of anticholinergic drugs used for urinary conditions in 540 people with dementia compared the risks between drugs with high and low or no central anticholinergic activity.10 Drugs with high central anticholinergic activity (oxybutynin and tolterodine) were associated with a relative increase in mortality of 55% (HR 1.55, 95% CI 1.19 to 2.01) compared with peripherally acting ones.11

Evidence of effect on cognition
There is increasing evidence of the more serious effects associated with drugs with anticholinergic activity in older people. In an observational study of 13,004 people aged ≥65 years, long-term use of drugs with anticholinergic activity was associated with a greater decline of 0.33 points in the Mini-Mental State Examination score and higher 2-year mortality (OR 1.68, 95% CI 1.30 to 2.16; p<0.001) than use of medication without anticholinergic activity.6

Large-scale observational studies have reported consistent associations between certain classes of drugs with anticholinergic activity and the incidence of dementia.11 A nested case–control study of patients aged ≥75 years (mean age 82 years, 63% female) in primary care in England assessed whether exposure to anticholinergic drugs was associated with dementia risk in 58,769 patients with a diagnosis of dementia and 225,574 matched controls.2 Compared with no anticholinergic use, the adjusted odds ratio for dementia was 1.06 (95% CI 1.03 to 1.09) in those exposed to the lowest level of anticholinergic activity and 1.49 (95% CI 1.44 to 1.54) with the highest level of exposure. Another case–control study used the UK Clinical Practice Research Datalink database to assess the association between the duration and level of exposure to different classes of anticholinergic drugs and subsequent incident dementia in people aged 65–99 years.7 The analysis included 40,770 cases and 283,933 controls (median age 83 years, 63% female) with a median drug exposure of 7 years. The adjusted odds ratio for any drug with an anticholinergic burden score of 3 (defined as a clinically relevant anticholinergic effect and reported association with delirium) was 1.11 (95% CI 1.08 to 1.14). Drugs that have been implicated include antidepressants, antipsychotics, drugs used for Parkinson’s disease, antiepileptic drugs and anticholinergic drugs used in urinary conditions.7,10

Anticholinergic burden

The anticholinergic burden is the cumulative effect on an individual taking one or more medicines with anticholinergic activity. Anticholinergic burden is associated with poor health outcomes as previously described. While it is not fully understood why certain drugs cause more harm than others, whether a drug penetrates the brain and affects cognition is determined by its physicochemical properties. A drug’s ability to cross the blood–brain barrier (BBB) is dictated by its polarity, molecular size and lipophilicity.12 In addition, the blockade of only certain muscarinic receptor subtypes is associated with cognitive impairment. Five muscarinic receptor subtypes have been identified (M1, M2, M3) and cognitive impairment, particularly memory dysfunction, have been suggested to result from antagonism of M1 receptors, and to some extent, M2 and M4 receptors in the CNS.13

Anticholinergic burden in older people
Older people are more vulnerable to the effects of medicines with anticholinergic activity due to reduced renal function and hepatic clearance, comorbidity diseases and decrease in cholinergic neurons and their receptors resulting in decreased transmission of acetylcholine within the central nervous system (CNS).5,9 In addition, certain conditions that occur in old age increase the permeability of the BBB including diabetes, Parkinson’s disease and Alzheimer’s disease.14 As a result, the BBB may allow drugs through that would not normally be able to penetrate. Furthermore, many conditions requiring treatment with anticholinergic drugs occur in advanced age (eg, urinary incontinence, Parkinson’s disease). As such, older people, especially those with multimorbidity and polypharmacy, are more likely to be taking multiple drugs with anticholinergic activity and are therefore at greater risk.15

Anticholinergic risk scales
To assist clinicians in identifying high-risk drugs and minimising their use in vulnerable people or those with cognitive impairment, various anticholinergic risk scales have been produced. These can be used to identify drugs with anticholinergic activity not obvious from their pharmacology. Such scales usually consist of a list of drugs with a classification of anticholinergic potency for each, allowing clinicians to calculate the total anticholinergic burden for an individual.16 Unfortunately, there is considerable variation among these scales because of differences in scale development, selection of drugs and methods of evaluating a drug’s anticholinergic potential. Two anticholinergic burden scales are widely used in the UK and have been clinically validated. The Anticholinergic Cognitive Burden (ACB) scale has been validated with various clinical outcomes, including cognitive impairment and physical functioning, and was used in many of the large-scale studies linking anticholinergic agents with increased risk of dementia.21 To be included, medications must have met the following criteria:

- ACB score of 1: evidence from in vitro data that the medication has antagonist activity at muscarinic receptors (eg, warfarin).
- ACB score of 2: evidence from literature, prescriber’s information or expert opinion of a clinical anticholinergic effect (eg, amantadine).
- ACB score of 3: evidence from literature, prescriber’s information or expert opinion of the medication causing delirium (eg, amitriptyline).22

An anticholinergic burden calculator, which uses a combination of the ACB scale and the German Anticholinergic Burden Scale (GABS), is available online (https://www.acbcalc.com/).23 The limitations of this scale are that BBB penetration is not always considered since all urinary drugs with anticholinergic activity are scored highly, irrespective of whether they penetrate the CNS or not. In addition, many of the drugs included in this list are not available in the UK and drugs that are not listed in those three categories cannot be deemed safe as it is not known whether they have been assessed or not.

The Anticholinergic Effect on Cognition (AEC) scale was designed primarily as a central anticholinergic burden scale. It allows the practitioner to easily identify which medicines can affect cognition and the size of the effect compared with other agents within a class.24 Hundreds of drugs commonly used in older people were ranked from 0 to 3 based on their individual physicochemical properties and ability to cross the BBB, such that different drugs from the same class may be allocated different AEC scores, thus, providing a safer choice of drug from within the same class of agents. The AEC has been validated with clinical outcomes in dementia including mortality and hospitalisation.25 Patients with dementia receiving medication with high AEC scores were found to have worse prognosis in terms of mortality and hospitalisation risk.21
As the risk of cognitive impairment, incident dementia and early death have been linked to the cumulative anticholinergic burden of drugs; it is good practice to keep the total anticholinergic burden or AEC score to a minimum. It is recommended that older people who are on medications with an individual AEC score ≥2 or have a total AEC score ≥3, have a medication review so that consideration can be given to suitable alternatives with a lower AEC score where available and appropriate. The aim is to reduce the total AEC score to the lowest possible value. The AEC scale can be accessed via the Medichec app at https://www.medichec.com/.

Some other available scales include the Drug Burden Index (DBI), which takes into account patients’ anticholinergic drug burden, sedative drug burden and total number of drugs; the Anticholinergic Drug Scale (ADS) based on literature reports of anticholinergic effects and clinicians’ rating of anticholinergic effect (0–3); and the Anticholinergic Risk Scale (ARS) which ranks drugs based on the drug’s affinity for the muscarinic receptor, experimental reporting of anticholinergic activity and literature review on anticholinergic adverse effects.

Comparison of risk scales
A recently published longitudinal analysis quantified 10 different scales (including ACB, AEC and ADS) with associated risks and outcomes in a cohort of 502,538 middle-to-older aged adults (aged 37–73 years) from the UK biobank who were followed up for a median of 6 years. Each participant’s baseline anticholinergic burden score was calculated using 10 different scales. The primary outcome was a composite of all-cause mortality and major adverse cardiovascular events (MACE) and secondary outcomes included

### Table 1 Drugs with high and low central anticholinergic activity

<table>
<thead>
<tr>
<th>Drug class</th>
<th>High central anticholinergic burden</th>
<th>Alternatives with low/no central anticholinergic burden</th>
</tr>
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<tbody>
<tr>
<td>Antidepressants*</td>
<td>Tricyclic antidepressants</td>
<td>SSRIs (except paroxetine)</td>
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<tr>
<td></td>
<td></td>
<td>Mirtazapine</td>
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<td></td>
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<td>Venlafaxine</td>
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<td>Agomelatine</td>
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<td>Moclobemide</td>
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<td>Duloxetine</td>
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<td>Vortioxetine</td>
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<td></td>
<td></td>
<td>Tranylcypromine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Chlorphenamine</td>
<td>Cetirizine</td>
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<tr>
<td></td>
<td>Promethazine</td>
<td>Loratadine</td>
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<td></td>
<td>Hydroxyzine</td>
<td>Fexofenadine</td>
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<tr>
<td></td>
<td>Cyproheptadine</td>
<td>(and other second generation antihistamines)</td>
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<tr>
<td></td>
<td>Cyclizine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(and other first generation antihistamines)</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics*</td>
<td>Clozapine</td>
<td>Aripiprazole</td>
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<td></td>
<td>Olanzapine</td>
<td>Amisulpride</td>
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<td></td>
<td>Quetiapine</td>
<td>Risperidone</td>
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<td></td>
<td>Zotepine</td>
<td>Lurasidone</td>
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<td></td>
<td>Chlorpromazine</td>
<td>Cariprazine</td>
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<tr>
<td>Antispasmodics</td>
<td>Atropine sulfate</td>
<td>Alverine</td>
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<td></td>
<td>Dicycloverine</td>
<td>Mebeverine</td>
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<td></td>
<td></td>
<td>Peppermint oil</td>
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<td></td>
<td></td>
<td>Hyoscine butylibromide (Buscopan)</td>
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<tr>
<td></td>
<td></td>
<td>Propantheline bromide</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>Hyoscine hydrobromide (Kwells)†</td>
<td>Pirenzepine†</td>
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<td></td>
<td></td>
<td>Atropine eye drops† (sublingually)</td>
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<tr>
<td>Drugs for Parkinson’s disease*</td>
<td>Trihexyphenidyl (benzhexol)</td>
<td>Co-beneldopa</td>
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<tr>
<td></td>
<td>Benzatropine†</td>
<td>Co-careldopa</td>
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<td></td>
<td>Amantadine</td>
<td>Entacapone</td>
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<td></td>
<td>Orphenadrine</td>
<td>Rasagiline</td>
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<tr>
<td>Drugs for urinary symptoms</td>
<td>Oxybutynin</td>
<td>Dusafenacine</td>
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<td></td>
<td>Tolterodine</td>
<td>Tropium</td>
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<td>Solifenacine</td>
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<td>Fesoterodine</td>
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*With regard to antidepressants, antipsychotic drugs and drugs used for Parkinson’s disease, it is not always possible to switch to an alternative agent with lower central anticholinergic activity. If a patient has been stable on a psychotropic drug for many years and is tolerating it well, it may not be appropriate to switch to an alternative drug simply based on its anticholinergic activity. Many other factors should inform this decision including a discussion with the patient and carers.

†Unlicensed.
‡Off-label.
SSRI, selective serotonin re-uptake inhibitors.
all-cause mortality, MACE, hospital admission for falls or fractures, and hospital admission for delirium or dementia. Depending on the scale used, anticholinergic prescribing ranged from 8% to 18%. A greater anticholinergic burden was associated with greater risk of the primary outcome for all the scales. Scales varied in the proportion of participants identified as taking anticholinergic medication and the size of the anticholinergic burden. In addition, there was considerable variation in the populations identified as being at risk between scales. The number of people identified as taking anticholinergics ranged from 40 000 to 90 000 across the 10 scales.31

ACB and ADS were strongly associated with mortality, whereas the AEC scale predicted mortality, but also, since it was designed to assess the risk of neurocognitive complications, showed the greatest effect size for dementia and delirium.71 It is not clear how often these scales are updated.32

Guidelines

In the UK, the National Institute for Health and Care Excellence (NICE) guideline on dementia and other national documents (eg, Dementia diagnosis and management: a brief pragmatic resource for general practitioners) recommends reviewing and minimising medicines associated with anticholinergic burden in people with dementia.33,34 NICE’s recommendations were based on a systematic review showing that higher anticholinergic burden was associated with negative brain effects, poorer cognitive and functional outcomes.21 Similarly, US guidance from the Beers Criteria lists anticholinergic drugs as potentially inappropriate medications which should be avoided in older adults where possible.35 As a result, health professionals are becoming more aware of the risks involved with these drugs and there is currently a national and international drive to minimise the use of anticholinergic medication in older people.36

Managing drugs with anticholinergic activity

Evidence supports the association between drugs with anticholinergic activity and the development of cognitive impairment, dementia or increased mortality in older people. Healthcare professionals are urged to consider the anticholinergic burden of a new drug before initiating it in an older person, and to try to find safer alternatives where possible. Anticholinergic burden scales can be used to identify high-risk drugs.

In addition, regular medication reviews should be undertaken in older patients, with a view to keeping the total anticholinergic burden to a minimum. Using either the ACB or AEC scale, reviews that lead to the identification of individual agents with an anticholinergic burden of ≥2, or a total anticholinergic burden score of ≥3 should prompt withdrawal or switching of the offending agents where possible.

Anticholinergic burden should also be assessed in any individual where there are concerns over cognitive function or the onset of delirium. If withdrawal of a drug is deemed appropriate, this should be gradual where possible to avoid rebound anticholinergic symptoms (eg, nausea, sweating, urinary frequency, diarrhoea).77 There is currently a lack of published studies looking at the development of interventions to reduce anticholinergic burden in older people, despite this being an area of high priority. Future research should focus on developing effective interventions to reduce anticholinergic burden and determining whether these interventions have an effect on the incidence of dementia as well as dementia outcomes.38

Before prescribing anticholinergic agents, the potential risks involved should be discussed with patients and carers. There are, of course, other considerations when balancing benefits and risks when considering prescribing of anticholinergic medications.

These drugs can be beneficial in improving symptoms as well as improving quality of life. Thus, careful risk versus benefit analyses should be made on an individual patient basis. Clinicians should be aware of the risks involved and the available tools to identify high-risk drugs, so that they are able to select safer alternatives where possible.

Table 1 lists the main classes of drugs that have anticholinergic activity and separates the drugs in terms of those with high central anticholinergic activity, based on the AEC scale, and those with low or no central anticholinergic activity. It should be noted that drugs with low/no central anticholinergic activity could still cause peripheral anticholinergic effects or cognitive effects through other mechanisms (eg, gamma-aminobutyric acid [GABA] inhibition).

Conclusion

There are considerable data suggesting an association between drugs with anticholinergic activity and serious adverse effects in older people. This includes several studies showing that long-term use of medicines with anticholinergic activity is associated with worsening of cognitive function, increased incidence of dementia and increased mortality. A range of rating scales have been devised to identify and calculate anticholinergic burden of medication. Although the scales vary in the proportion of participants identified as taking anticholinergic medication, the size of the anticholinergic burden and the number of people identified as being at risk of anticholinergic effects, greater anticholinergic burden is associated with greater risk of adverse effects.

Healthcare professionals should assess anticholinergic burden in older people and those at higher risk of anticholinergic adverse effects and consider using lower-risk alternative medication where possible. Future research should focus on the effect of reducing anticholinergic burden on clinical outcomes.

Information for patients

► Medicines with anticholinergic activity block the action of the chemical acetylcholine.
► Medicines with anticholinergic activity are used to manage a wide range of conditions, including urinary symptoms and incontinence, irritable bowel syndrome, depression, psychosis, chronic obstructive pulmonary disease and Parkinson’s disease.
► Side effects of medicines with anticholinergic activity include dry mouth, blurred vision, urinary retention, constipation, confusion, disorientation, memory impairment, hallucinations and delirium.
► Some studies have shown that long-term use of medicines with anticholinergic activity is associated with serious adverse effects including an increased risk of dementia.
► It is important that a healthcare professional regularly reviews your medicines to ensure that they are appropriate for you and to minimise the use of medicines with anticholinergic activity where possible.
► If you have any concerns about medicines with anticholinergic activity you should discuss them with your doctor or pharmacist.

Competing interests None declared. Refer to the online supplementary files to view the ICMJE form(s).

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