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USE OF MEDICINES WITH ANTICHOLINERGIC ACTIVITY

- **Many medicines that are commonly used in clinical practice are associated with anticholinergic activity**
- **The use of medicines with high anticholinergic activity is associated with an increased risk of adverse clinical outcomes for patients, especially older patients**
- **Anticholinergic scales can be used to identify medicines with anticholinergic activity and to assess the anticholinergic burden for an individual patient**
- **The anticholinergic activity of a medicine should be considered when initiating medicines in older people, and the total anticholinergic burden assessed at medication review or if there are concerns regarding cognitive function**

INTRODUCTION

Medicines with anticholinergic activity are commonly prescribed for a wide range of conditions including bladder disorders, obstructive respiratory disorders, Parkinson's disease, depression, hypertension, cardiovascular disease, psychotic symptoms, behavioural problems and allergies.[1,2] While medicines with anticholinergic activity are effective for many conditions, it is important to be aware of the risks associated with their use, especially in the older population (i.e. those aged ≥65 years).[3] In addition to anticholinergic medicines being associated with short-term adverse effects (e.g. dry mouth, blurred vision, dizziness and confusion), increasing evidence is emerging of more long-term adverse effects, such as an increased risk of cognitive decline, dementia and early death.[1,4,5] Individual medicines have different levels of anticholinergic activity, and the risk of an adverse event is higher and is cumulative when more than one medicine with anticholinergic properties is prescribed. This is known as the anticholinergic burden.[3] The prevalence of prescribing anticholinergic medicines is increasing; a UK cohort study of >200,000 participants reported a 9-fold increase in anticholinergic burden from 1990 to 2015.[6] The increase was attributed to increasing polypharmacy (commonly defined as co-administration of ≥5 medicines), ageing of participants and changes in prescribing practices.[6]

This bulletin will review the adverse effects of anticholinergic medicines, outline the tools available to measure an individual's anticholinergic burden, and provide practical guidance to minimise excess anticholinergic exposure in vulnerable patients.

A BRIEF LOOK AT PHARMACOLOGY

The autonomic nervous system has three distinct divisions, one being the parasympathetic nervous system, of which acetylcholine (ACh) is the chief neurotransmitter.[7,8] Medicines that increase parasympathetic activity are used in the treatment of Alzheimer's disease, glaucoma, myasthenia gravis, and urinary and intestinal stasis. On the other hand, medicines that decrease parasympathetic activity (medicines with anticholinergic activity) are used in the treatment of overactive urinary and intestinal conditions, asthma and chronic obstructive pulmonary disease (COPD), motion sickness and during various ophthalmic procedures.[8]

Table 1 gives examples of medicines with strong anticholinergic activity.

Table 1: Examples of medicines with strong anticholinergic activity[12]

Therapeutic area	Examples of medicines*
Antidepressants	Amitriptyline, clomipramine, nortriptyline, paroxetine
Antipsychotics	Chlorpromazine, clozapine, olanzapine, quetiapine, risperidone, haloperidol
Antiemetics	Prochlorperazine, promethazine
Urinary antispasmodics	Oxybutynin, tolterodine, fesoterodine, flavoxate, solifenacin, trospium chloride
Antihistamines	Chlorphenamine, promethazine, hydroxyzine, brompheniramine, dimenhydrinate, diphenhydramine, doxylamine
Parkinson's disease	Benzatropine
Antispasmodics	Atropine, hyoscine hydrobromide

* this table is not a comprehensive list of all medicines with anticholinergic properties

Medicines with anticholinergic activity antagonise the action of ACh by binding to muscarinic receptors.[1,9,10]

Muscarinic receptors are widely distributed in the body, which results in the wide range of effects seen with anticholinergic medicines.[7,10,11] There are five muscarinic ACh receptors (M_1 to M_5);[5] generally M_1 is expressed in cortical neurons and autonomic ganglia, M_2 in cardiac muscle, M_3 in smooth muscle and M_4 and M_5 in the central nervous system (CNS).[7]

it is important to note that some medicines are available over-the-counter (OTC), e.g. chlorphenamine and promethazine.[7] While some medicines are used primarily for their anticholinergic action, others have secondary, often unintended, anticholinergic effects.[9]

ADVERSE EFFECTS OF ANTICHOLINERGIC MEDICINES

The adverse effects associated with anticholinergic medicines occur due to excessive blockade of the parasympathetic nervous system.[8] **The likelihood of an anticholinergic adverse effect occurring depends on the patient as well as the properties of the individual medicine such as the dose, the bioavailability, the ability of the drug to cross the blood brain barrier (BBB), the permeability of the patient's BBB and the binding affinity of the drug to different muscarinic receptors.**[10,11] Some medicines may have limited anticholinergic effects when used alone, but may have clinically significant anticholinergic effects if used in combination with other anticholinergic medicines.[2] Therefore, the risk of an adverse effect occurring is increased by polypharmacy.[2]

The anticholinergic adverse effects can be categorised as peripheral and central, dependant on the drug's ability to pass the BBB.[1,4,13] Peripheral adverse effects include dry mouth, nausea, vomiting, constipation, blurred vision, diplopia, tachycardia and urinary retention, while central adverse effects include dizziness, headache, drowsiness, nervousness, numbness, mental confusion and/or excitement (especially in older people), dyskinesia, lethargy, syncope, speech disturbance and insomnia.[1,2,10]

Toxic doses of anticholinergic medicines can result in hyperpyrexia and severe CNS depression, which may result in respiratory depression and death.[1]

In addition to the adverse effects described above, evidence is also emerging that long-term use of medicines with anticholinergic activity is associated with an increased risk of mortality, cognitive impairment and falls.[5] Note that the majority of the evidence is from observational studies, which have different designs and methods, including the use of different scales/criteria to identify anticholinergic medicines and anticholinergic burden.[14] For example, some studies reported positive associations with dementia using certain scales but not with other scales[15,16] (see section "Anticholinergic risk scales" for further details).

Effects on mortality: Evidence from observational studies suggests that medicines with anticholinergic activity and/or a high anticholinergic burden are associated with higher mortality rates and an increased risk of cardiovascular events.[11,17,18] Some of the studies reported a dose-response relationship.[9,17-19]

Effects on cognition: Evidence from observational studies increasingly suggests that long-term exposure to anticholinergic medicines and/or high anticholinergic burden is associated with cognitive impairment (including mild cognitive impairment, delirium and dementia),[11,15,16,19-25] although not all studies report this association.[14,26] A recent Cochrane systematic review of observational studies suggests correlation between use of anticholinergic drugs and future risk of dementia, but it did not prove causation.[27]

The role of the central cholinergic system in cognitive impairment was discovered more than 30 years ago.[2] Ageing may result in cholinergic deficits in the CNS, which increases the older person's sensitivity to medicine-related cognitive effects and is also considered to contribute substantially to the cognitive impairment and behavioural symptoms seen in patients with dementia.[1,2,4] Evidence suggests that cognitive impairment results from antagonism of M_1, M_2 and M_4 receptors,[5] which is more likely to occur with medicines that cross the BBB.[1,5]

Cholinesterase inhibitors were developed to increase the availability of ACh in the brain, and are used in the management of Alzheimer's disease and Parkinson's disease dementia.[2,4] It is estimated that up to half of patients with Alzheimer's disease who are prescribed cholinesterase inhibitors are also taking medicines with anticholinergic activity,[28,29] and it is important to note that medicines with anticholinergic activity directly oppose the action of cholinesterase inhibitors.[5]

Effect on falls risk: Some observational studies have also reported an association between use of anticholinergic medicines in older people and an increased risk of falls.[14,30,31]

USE OF ANTICHOLINERGIC MEDICINES IN OLDER ADULTS

Drug-related anticholinergic adverse effects are potentially hazardous to older patients, especially those with cognitive impairment; they cause significant morbidity in this population.[7] The additive effects of anticholinergic medicines can increase the risk of adverse effects in older people as 1) many common medicines may have some anticholinergic activity, 2) the older person and especially those with cognitive impairment are more sensitive to cholinergic blockade (due to central cholinergic hypofunction and dysfunction in ageing and dementia, respectively) and 3) polypharmacy is common in the older population, and may include OTC medicines.[1,2,4,7,9,11]

Age-related physiological changes include reduced renal and hepatic function with potential impact on drug elimination, changes in body mass distribution of medicines, a decrease in cholinergic neurons and receptors, and increased BBB permeability.[1,2,9,13,16]

Older people are commonly prescribed medicines with anticholinergic effects; evidence suggests that at least 50% of older people (age ≥65 years) use ≥1 anticholinergic medicine.[2,4,13,32,33] In the nursing home setting, there is some evidence to suggest that up to 30% of residents take >2 anticholinergic drugs and 5% take >5.[34] A study undertaken in England reported that the prevalence of strong anticholinergic medicines nearly doubled (from 5.7% to 9.9%) in the previous two decades in those aged ≥65 years, with the greatest increase seen in older people with clinically significant cognitive impairment.[35] It is estimated that one third to one half of the most commonly prescribed drugs for older people have anticholinergic properties.[36] The prevalence of polypharmacy is also increasing;[37,38] an Irish study reported that the prevalence of polypharmacy increased from 17.8% to 60.4% in those aged ≥65 years, from 1997 to 2012.[38]

It is important to try to minimise polypharmacy in the older population and to monitor and prevent medication-related anticholinergic adverse effects.[7] Particular caution should be considered when prescribing medicines with strong anticholinergics effects such as first-generation antihistamines (e.g. diphenhydramine), antidepressants with strong anticholinergic activity (e.g. amitriptyline, paroxetine), antiparkinsonian agents with strong anticholinergic activity (e.g. benzatropine), antimuscarinic agents used for urinary incontinence (e.g. oxybutynin), and antispasmodics with high anticholinergic activity (e.g. hyoscine hydrobromide).[7,12]

ANTICHOLINERGIC RISK SCALES

The importance of considering the use of medicines with anticholinergic activity especially in the older population, has led to the development of tools, such as anticholinergic risk scales; these estimate the overall anticholinergic drug burden for an individual.[1,4,10] There are several validated anticholinergic risk scales used in research and in clinical practice.[9,13] Scales have been validated in outcomes including delirium, cognition, mortality and falls. There is a lack of standardisation in the way in which the scales were developed, for example, around the number medicines selected and the method for evaluating anticholinergic activity,[5,39] and this should be considered when interpreting the study results (may differ depending on the scale used).[5] For example, a review of 18 scales reported that of 195 medicines that were categorised by the different scales, 17% were scored differently in various scales, and 6% were scored as having low anticholinergic effect in at least one scale, but having high anticholinergic activity in another.[14]

A number of reviews have assessed the various rating scales;[13,14,39-44] the consensus is that no one anticholinergic scale is recognised as the gold standard. Table 2 summarises the characteristics of some commonly used anticholinergic burden scales.[13]

Table 2: Characteristics of some anticholinergic burden scales[13,14]

Tool	Method of assessment of anticholinergic burden
Anticholinergic Cognitive Burden Scale (ACB)	Expert committee, receptor binding/SAA, anticholinergic adverse drug effect, BBB permeability
Anticholinergic Drug scale (ADS)	Expert committee, receptor binding/SAA, anticholinergic adverse drug effect
Anticholinergic Effect on Cognition Scale (AEC)	Expert committee, receptor binding/SAA, anticholinergic adverse drug effect, BBB permeability
Anticholinergic Risk Scale (ARS)	Expert committee, receptor binding/SAA, anticholinergic adverse drug effect
Duran scale	Receptor binding/SAA, anticholinergic adverse drug effect, BBB permeability, dose consideration, drug interaction
German Anticholinergic Burden Scale (GABS)	Expert committee, receptor binding/SAA, anticholinergic adverse drug effect, BBB permeability, dose consideration, drug interaction
Drug Burden Index (DBI)	Uses Mosby's Drug Consult and the Physicians' Desk Reference

BBB-blood brain barrier; SAA-serum anticholinergic activity

Even though there are differences in the various scales, anticholinergic burden scores may be a useful guide for assessing the potential risk of anticholinergic adverse events occurring, however they should not be considered in isolation.[3,39] In general, anticholinergic scales usually rank the anticholinergic activity of medicines into four categories ranging from 0 to 3:[9,13,26,40]

- (0) - no known or limited anticholinergic activity
- (1) – minimal, weak or mild anticholinergic activity
- (2) – some or moderate anticholinergic activity
- (3) – strong anticholinergic activity

The anticholinergic burden for an individual patient (the cumulative effect of taking multiple medicines with anticholinergic effects) is calculated by adding the anticholinergic activity scores of each medicine.[1,4,9,13] The Anticholinergic Cognitive Burden (ACB), the German Anticholinergic Cognitive Burden Scale (GABS) and the Anticholinergic Effect on Cognition (AEC) scales are commonly used scales that give advice on the application to clinical practice.[13] The ACB online calculator is a combination of the ACB and GABS that is freely available; a limitation of this scale is that BBB penetration is not always considered.[4]

The AEC scale was designed primarily as a central anticholinergic burden scale; table 3 gives examples of medicines classified as having an AEC score of 1, 2 or 3 (the list of medicines is not exhaustive and additional medicines and categories using this scale are available on medichec.com).

Table 3: Anticholinergic effect (AEC) on cognition scores of some medicines with capacity to impair cognitive function[5,45]*

Medicines with AEC score of 1	Medicines with AEC score of 2	Medicines with AEC score of 3
Amiodarone	Amantadine	Amitryptyline
Aripiprazole	Chlorphenamine	Atropine
Bromocriptine	Dicycloverine	Benzatropine
Carbamazepine	Dimenhydrinate	Chlorpromazine
Citalopram	Diphenhydramine	Clomipramine
Diazepam	Disopyramide	Clozapine
Domperidone	Levomepromazine	Dothiepin
Fentanyl	Olanzapine	Hyoscine hydrobromide
Fluoxetine	Paroxetine	Lofepramine
Hydroxyzine	Pethidine	Nortriptyline
Lithium	Prochlorperazine	Oxybutynin
Mirtazapine	Quetiapine	Procyclidine
Prednisolone	Tolterodine	Promethazine
Quinidine	Trifluoperazine	Trimipramine
Sertraline		
Solifenacin		
Temazepam		

*this list is not exhaustive; additional categories and medicines are available on https://medichec.com/

PRACTICAL ASPECTS

It is recommended that the use of anticholinergic medicines should be minimised in older people, and alternatives used when appropriate.[4,6,12,46,47] An awareness of the anticholinergic effects associated with specific medicines and of their potential adverse effects especially in the older population, is important to optimise prescribing and prevent iatrogenic harm.[3,11] Evidence supports the use of medication reviews to reduce the anticholinergic burden and the use of anticholinergic medicines.[48] Evidence also suggests that the deprescribing of anticholinergic medicines reduces the risk of falls and other adverse drug reactions.[49]

While there is variation in the different anticholinergic risk scales, they can be useful to calculate a patient's anticholinergic burden score and thereby identify patients at risk of anticholinergic–related adverse events.[1,9,50] It is important, however, that the anticholinergic burden is not considered in isolation, but in the context of other prescribing practices such as polypharmacy and the appropriateness of the individual medicine for the patient.[6] **Anticholinergic risk scales can be used in association with other tools such as the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria to help optimise prescribing and decision making especially in the older population.**

The assessment of the anticholinergic effect of a medicine and the cumulative total anticholinergic burdens should be considered when initiating a medicine or when conducting a medication review (including OTC medicines) in an older person, and/or where there are concerns about cognitive function in a patient.[2-4]

The benefit/risk of initiating or continuing an individual medicine with an anticholinergic burden of ≥2 or in patients with a total anticholinergic burden of ≥3 should be assessed.[1,2,4,23] Discontinuation or switching to an alternative medicine may be considered for medicines when there is an anticholinergic burden of ≥2,[4] especially if the medicine is ineffective after an adequate trial or where adverse effects exist that outweigh the benefits.[3] If appropriate, the use of a medicine with no or low anticholinergic activity, or with high specificity to the site of action and with minimal CNS activity should be considered as an alternative (e.g. the use of mirabegron or solifenacin [which has less central anticholinergic activity than oxybutynin] for the management of urinary symptoms).[1,3,4] Other factors may also influence the anticholinergic burden e.g. the dose of the medicine and the patient's renal function.[3]

Patients discontinuing anticholinergic medicines may experience symptoms such as nausea, sweating, agitation, confusion and urinary urgency.[3,51] The gradual withdrawal (i.e. tapering) of a medicine may be required to avoid rebound anticholinergic or psychiatric effects.[2,3] **In general, the longer the patient has been on an anticholinergic medicine, the longer the period of withdrawal that is required.[51]** Specialist input may be required in individual circumstances.

In addition, **it is important to consider that in certain conditions (e.g. Parkinson's disease) and with certain medicines (e.g. antidepressants and antipsychotic medicines), it is not always possible or appropriate to switch to an alternative medicine with lower central anticholinergic activity, especially if the patient has been stable on the medicine for many years and is tolerating it well.[4]** Similarly in palliative care, the use of medicines with anticholinergic activity such hyoscine hydrobromide may be useful in terms of symptom control.[52]

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