A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

ANTICHOLINERGICS

KEY POINTS

Anticholinergic medicines encompasses a variety of medicines that can be used for many indications, such as urinary incontinence, anxiety, depression, Parkinson's disease, respiratory conditions, and allergies.

Medicine with anticholinergic effects can differ in their anticholinergic load and can be classed as high or low potency anticholinergics.

Some examples of commonly used medicines with anticholinergic effects include SSRIs, oxycodone, pregabalin and levodopa.

The use of multiple medicines with anticholinergic effects can contribute to anticholinergic burden. This burden often occurs through use of multiple low potency anticholinergics.

A high anticholinergic burden increases the risk of dementia and cognitive decline, falls and mortality.

Anticholinergics can interfere with cholinesterase inhibitor treatment, potentially worsening dementia symptoms.

Cessation of anticholinergic medicines should be done gradually, in order to reduce the risk of withdrawal effects.

CONTEXT

This guide considers the use of systemic anticholinergics in the older population.

RECOMMENDED DEPRESCRIBING STRATEGY

- Estimate overall Anticholinergic Burden (ACB) by either using a ACB calculator or the information provided in Table 1. If using a calculator, it is preferable to use one that takes dosages of anticholinergic medicines into account. A good example of a ACB calculator can be found here: http://www.anticholinergicscales.es/
- Target higher potency anticholinergics first, as these will have the highest anticholinergic load and will have a larger contribution to the overall ACB.
- The use of multiple lower potency anticholinergics can also commonly lead to an increased ACB.

BACKGROUND

Anticholinergic medicines (also referred to as muscarinic antagonists) competitively inhibit the transmission of acetylcholine by antagonizing muscarinic receptors in both the central and peripheral nervous systems.[1] Whilst some medications may be prescribed specifically for their anticholinergic actions, others may possess anticholinergic activity that is unrelated to their therapeutic effect.[2]
Anticholinergic medicines and medicines with anticholinergic effects can be prescribed for a wide variety of conditions such as urinary incontinence, Parkinson's disease, schizophrenia, anxiety, and depression. The clinical utility of these drugs, may in some cases, be limited by their adverse effects.[3]

The use of anticholinergics in the older population is particularly concerning. Not only are the elderly more prone to short term adverse effects such as constipation and dry mouth, but the long term and cumulative use of such agents can lead to increased risk of falls, cognitive impairment, dementia and mortality. In view of these risks it is broadly accepted that these drugs should be avoided in the older population where possible.[4] Various anticholinergic medicines have been identified as potentially inappropriate medications for use in older adults, as per the BEERS and STOPP criteria.[5] Despite this, they are still widely prescribed, with 21-34% of older Australians using medicines with anticholinergic effects[6] and 20-50% of older adults prescribed at least one anticholinergic medicine.[7]

MEDICINES WITH ANTICHOLINERGIC EFFECTS

Whilst some medicines have a mode of action that is primarily anticholinergic, there are many other medicines with anticholinergic effects alongside other pharmacological properties.[3]
Table 1 outlines the groups of commonly used medicines and their anticholinergic burdens.[8]

[1] List is not exhaustive

[2] Anticholinergic Burden was calculated using the anticholinergic calculator available here: http://www.anticholinergicscales.es/

[3] Medicines marked with * were calculated manually using formula [(dose/(minimum effective dose + dose)]. Minimum effective doses were obtained from Australian approved product information available on TGA website.

Class	ACB scores	Medicines (oral unless otherwise stated)
Antidepressants	<0.5	amitriptyline 10mg (0.29), sertraline 25mg (0.33), venlafaxine 37.5mg (0.33)
	0.50-0.60	escitalopram 10mg (0.50), fluoxetine 20mg (0.50), fluvoxamine 100mg (0.50)*, paroxetine 20mg (0.50), sertraline 50mg (0.50), desvenlafaxine 50mg (0.50)*, duloxetine 60mg (0.50)*, amitriptyline 25mg (0.50), agomelatine 25mg (0.50)*, moclobemide 300mg (0.50)*, reboxetine 8mg (0.50)*, venlafaxine 100mg (0.57)
	0.60-0.80	citalopram 20mg (0.67), amitriptyline 50mg (0.67), mianserin 60mg (0.67)*, vortioxetine 10mg (0.67)*, dosulepin (dothiepin) 150mg (0.67), amitriptyline 75mg (0.75), doxepin 100mg (0.8),
	>0.80	nortriptyline 75mg (0.88), clomipramine 100mg (0.91), imipramine 100mg (0.91)
Opioids	0.25-0.60	buprenorphine 15mcg/hr (transdermal) (0.25)*
	0.5- 0.60	oxycodone 20mg (0.50), fentanyl 12mcg (transdermal) (0.50)
	0.60-0.80	tramadol 300mg (0.67), tapentadol 100mg (0.67)*, morphine 20mg (0.67), oxycodone 75mg (0.79)
	>0.80	methadone 25mg (0.83), hydromorphone 20mg (0.83), morphine 100mg (0.91)
Gabapentinoids	<0.5	pregabalin 50mg (0.25)
	0.5-0.60	pregabalin 150mg (0.50)
	0.60-0.80	pregabalin 300mg (0.67), gabapentin 900mg (0.75)
	>0.80	gabapentin 1800mg (0.86)
Benzodiazepines	<0.50	oxazepam 7.5mg (0.43), clonazepam 1mg (0.40)
	0.50-0.60	flunitrazepam 1mg (0.50)*, nitrazepam 5mg (0.50)*, temazepam 10mg (0.5)*, lorazepam 1mg (0.50)
	0.60-0.80	temazepam 20mg (0.67)*, oxazepam 15mg (0.67), diazepam 10mg (0.71), lorazepam 2.5mg (0.71)
	>0.80	oxazepam 30mg (0.80), clonazepam 8mg (0.84)
Antipsychotics	<0.50	haloperidol 0.5mg (0.25), risperidone 0.25mg (0.33), quetiapine 25mg (0.33)
	0.50-0.60	amisulpride 400mg (0.50)*, risperidone 0.5mg (0.5), aripiprazole 15mg (0.60), brexpiprazole 3mg (0.60)*, lurasidone 60mg (0.60)*
	0.60-0.80	asenapine 20mg (0.67), olanzapine 10mg (0.67), paliperidone 6mg (0.67), ziprasidone 80mg (0.67), risperidone 1mg (0.67)
	>0.80	haloperidol 8mg (0.84), quetiapine 400mg (0.89), risperidone 5mg (0.91), chlorpromazine 300mg (0.92), clozapine 300mg (0.96)
Antiparkinsonian drugs	<0.5	levodopa with a decarboxylase inhibitor 150mg (0.20)*, pramiprexole 0.125mg (0.32)
	0.5-0.6	pramiprexole 0.25mg (0.49)
	0.60-0.80	levodopa with a decarboxylase inhibitor 600mg (0.67)*
	>0.80	benztropine 2mg (0.80)
Antihistamines	<0.50	promethazine 25mg (0.29)*
	0.50-0.60	loratadine 10mg (0.50), fexofenadine 120mg (0.50)*, dexchlorpheniramine 6mg (0.50), cetirizine 10mg (0.50), promethazine 25mg (0.50)*
	0.60-0.80	fexofenadine 180mg (0.60)*, doxylamine 25mg (0.67), cyproheptadine 12mg (0.75), diphenhydramine 200mg (0.80), doxylamine 50mg (0.80)
	>0.80	
Urinary anticholinergics	<0.50	oxybutynin 5mg (0.25)
	0.50-0.60	oxybutynin 15mg (0.50), darifenacin 7.5mg (0.50)*, solifenacin 5mg (0.50), tolterodine 4mg (0.50)
	0.60-0.80	propantheline 60mg (0.73)
	>0.80	
Gastrointestinal drugs	<0.50	domperidone 10mg (0.17), metoclopramide 10mg (0.25)
	0.50-0.60	domperidone 30mg (0.50)*, prochlorperazine 15mg (0.50)*, loperamide 2mg (0.50)
	0.60-0.80	metoclopramide 30mg (0.75)
	>0.80	loperamide 10mg (0.83)

Table 1: Anticholinergic load (ACB) of commonly used medicines

ADVERSE EFFECTS

Opthalmological	
Mild/moderate	Severe
Dry eyes	Visual disturbances
Accommodare insufficiency	Exacerbation and/or precipitation of acute angle closure glaucoma
Blurry vision	

Central Nervous System	
Mild/moderate	Severe
Confusion	Hallucinations
Drowsiness	Delirium
	Cognitive impairment (exacerbated in patients with dementia)
	Increased risk of falls and fractures

Dermatological	
Mild/moderate	Severe
Reduced sweating	Hyperthermia
Rash	

Cardiovascular	
Mild/moderate	Severe
Tachycardia	Exacerbation of angina
Postural hypotension	Myocardial infarction
	Worsening of heart failure

Lower Gastrointestinal Tract	
Mild/moderate	Severe
Constipation	Gastrointestinal obstruction
Nausea	Faecal impaction
	Paralytic ileus

Upper Gastrointestinal Tract	
Mild/moderate	Severe
Dry mouth	Dental decay
Reduced saliva production	Misfitting dentures
Thirst	Difficulty with speech
Reduced appetite	
Difficulty chewing and/or swallowing	
Dyspepsia	

Genitourinary Tract	
Mild/moderate	Severe
Urinary hesitancy	Urinary retention
Incontinence	Urinary tract infections

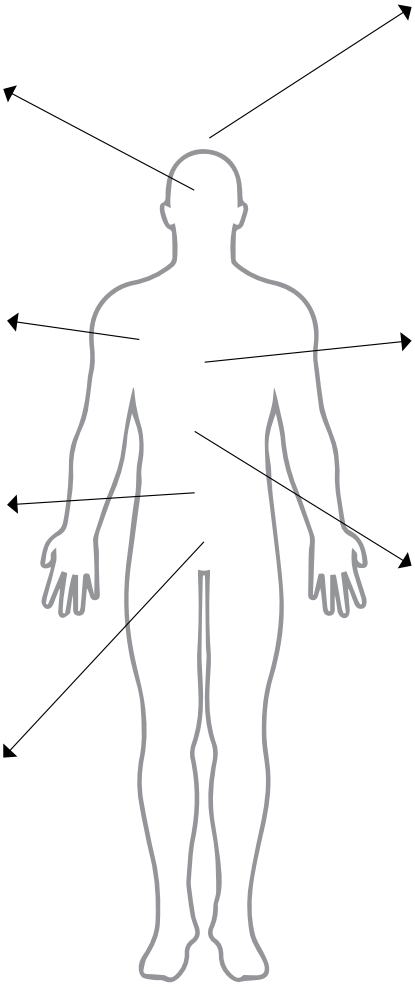

Figure 1: Anticholinergic effects in the body (modfied from references 2,9,11)

As cholinergic transmission is involved in various bodily functions in both the central and peripheral nervous systems, a range of adverse effects can occur.[3] Central adverse effects occur more frequently with anticholinergic drugs that readily cross the blood brain barrier (BBB) (e.g. oxybutynin).[9,10] Although some of these adverse effects may be mild/moderate, they can potentially be more severe.

Older adults are more susceptible to anticholinergic effects due to both age-related pharmacokinetic (e.g. reduced liver and renal function) and pharmacodynamic changes (e.g. decreased central cholinergic transmission, increased permeability of BBB).[1,11] Older adults are more likely to present with multiple comorbidities and therefore be prescribed multiple medicines with anticholinergic effects for conditions such as COPD, Parkinson's disease, allergies, depression, psychosis and urinary incontinence.

ANTICHOLINERGIC BURDEN (ACB)

The use of multiple medications that exert anticholinergic effects can lead to a cumulative effect, increasing the risk of adverse effects and is commonly referred to as the ACB. A higher ACB is associated with impaired cognitive and physical function, cardiovascular events, falls, fractures, hospital admissions, reduced quality of life and mortality.[12,13]

There are various anticholinergic risk scales that exist that are used to estimate ACB. These scales often utilize a 3-point grading system to quantify anticholinergic load of different medicines, from 0 (none) to 3 (strong), with the total ACB determined by summating all scores. Examples of validated ACB scales are Anticholinergic Drug Scale (ADS), Anticholinergic Cognitive Burden Scale (ACBS), Anticholinergic Risk Scale (ARS) and the Drug Burden Index (DBI).[6,14]

More than 600 drugs have some degree of anticholinergic activity, and can be categorized into groups according to their anticholinergic load.[9] Although high potency anticholinergics have a higher anticholinergic load (ultimately leading to an increased ACB), it is important to remember that using a combination of low potency anticholinergics can lead to a significant cumulative ACB.[12,15]

DEMENTIA AND COGNITIVE DECLINE

Anticholinergic medicines have been consistently associated with cognitive decline in individuals with and without dementia[16]

Adults without dementia

Older adults with no cognitive impairment that are prescribed potent anticholinergic medicines are twice as likely to develop cognitive decline and dementia in comparison to non-users, irrespective of age, sex and comorbidities. A higher ACB potentially increases the risk of future cognitive decline and dementia by more than 2-fold (see **Table 2**).[7]

Anticholinergic Burden	OddsRatio for Cognitive Decline
1	2.18
2	2.71
3	3.27

Table 2: Relationship of Anticholinergic Burden Score and Future Cognitive Decline (adapted from Ref 6)

A population-based prospective cohort study in the United States, involving over 3000 participants over the age of 65, associated the use of potent anticholinergics with incident dementia over the course of a 10 year period.[17] This study found the most commonly used drugs with anticholinergic effects were antidepressants, antihistamines and urinary antimuscarinics, with these three classes accounting for over 90% of anticholinergic exposure. Similar results were found in a nested case control study from 2019, involving over 280,000 participants, which showed that cumulative use of potent anticholinergics were associated with an increased risk of dementia (adjusted HR 1.65), with the highest risk associated with antidepressants, antipsychotics, antiepileptics and urinary antimuscarinics.[18]

Although it is clear there is growing evidence linking anticholinergics with onset of dementia and cognitive decline, it is worth acknowledging that the degree of this association is difficult to determine due to the risk of reverse causation and bias, particularly if drugs with anticholinergic effects are prescribed for management of prodromal signs of dementia (e.g. insomnia, depression, anxiety) as any risk association can be exaggerated as a result.[7]

Adults with dementia

Adults with mild to moderate Alzheimer's disease can experience further significant cognitive decline when using anticholinergic medicines.[16] In patients taking cholinesterase inhibitors such as donepezil, a high ACB has the potential to cause a rapid decline in dementia symptoms. A 2018 retrospective cohort study based in Korea, involving 825 participants, analysed the effect of a high ACB on the use of cholinesterase inhibitors for treatment of dementia. The results showed that approximately 6% of participants prescribed cholinesterase inhibitors had a high ACB (>3), adversely affecting the expected response and resulting in treatment modification increasing the risks of delirium and or mortality by 52% and 23% respectively.[19]

FALLS

Anticholinergic agents can contribute to an increased risk of falls, via their impacts on the CNS (e.g. drowsiness, ataxia, cognitive impairment) and other effects such as mydriasis that can result in blurry vision.[20] Exposure to an increased ACB increases the risk of falls and subsequent hospital admissions by 60%.[6]

A higher ACB may also cause deficits in gait speed and simple manual response time, both indicators of balance problems and falls in older adults.[21] An analysis of over 900 participants aged over 65 years in the Women's Health and Aging study in the United States demonstrated that the use of anticholinergic medicines was associated with a reduction in balance and mobility.[22]
A prospective cohort study of over 60,000 post-menopausal women investigated the association between anticholinergic use and recurrent falls. At baseline, 11.3% of participants were prescribed anticholinergic medicines, with the most common being antihistamines. The findings were that long term use of anticholinergic medicines significantly increased the risk of recurrent falls (adjusted odds ratio 1.51, 95% CI, 1.43-1.60). Participants who were taking multiple anticholinergic medicines had an even higher risk of recurrent falls (adjusted odds ratio 2.00, 95% CI 1.73-2.32).[23]

Similarly, a study investigating the association between ACB and falls in residential aged care facilities (RACFs) in Sydney, Australia, found that a higher ACB was significantly and independently associated with an increased risk of falls. After adjusting for factors such as age, sex, history of falls, incontinence, use of walking aids, age, sex and polypharmacy, incident rate ratios for falls were found to be 1.61 (95% CI=1.17-2.23) for low DBI scores (<1) and 1.90 (95% CI=1.30-2.78)for high DBI scores (≥1).[24]

MORTALITY

An increased ACB and sedative burden can result in a 30% increased risk of mortality in the older population.[6] An observational study from 2015 examined the link between ACB on mortality and cardiovascular disease (CVD) in over 21,000 participants. The results found that participants with a higher ACB had an increased risk of mortality and CVD events in comparison to participants with lower ACBs[26] (see **Figure 2**).

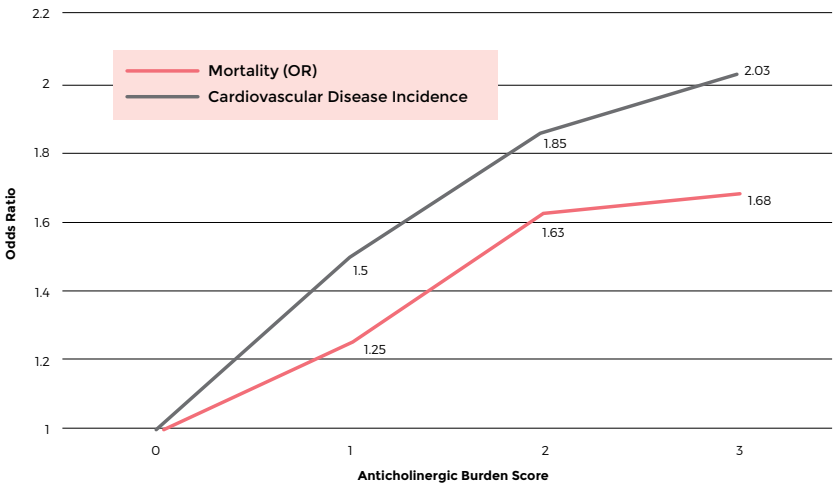

Figure 2: Anticholinergic Burden Score, Mortality and Cardiovascular Disease incidence (Adapted from Ref 27)

FACTORS TO CONSIDER

FACTORS TO CONSIDER BEFORE DEPRESCRIBING

Currently, there are no guidelines or position statements specifically for deprescribing to reduce ACB.[6] However, there are deprescribing guides for particular classes of medicines with anticholinergic effects, including antipsychotics, benzodiazepines, urinary antimuscarinics, opioids and antihistamines.[25] A 2019 New Zealand study of aged care facility residents demonstrated that there can be a variety of benefits when deprescribing anticholinergic medicines. This used a collaborative approach, involving pharmacists and general practitioners in medication review. The results showed a significant median decrease of 0.34 in patient's DBI scores 6 months after deprescribing anticholinergics. The number of adverse effects and falls were reduced, and both depression and frailty scores were reduced 6 months post-deprescribing.[6,26]

When deprescribing anticholinergic medicines, it is important to assess the impact of dose-dependency. Whilst ACB results from the potency of anticholinergic medicines, the administered dosages also play a role, with higher dosages leading to increased risk of both short term and long term adverse effects.[6,27] Taking both potency and dosage into consideration allows for a more comprehensive assessment of anticholinergic load.[28]

IN FAVOUR OF DEPRESCRIBING

- Patients with dementia who are prescribed cholinesterase Inhibitors are at a higher risk of rapid cognitive decline and subsequent treatment modification due to the antagonistic effects of anticholinergics.
- Patients at a high risk of falls, particularly if other sedating medications are used concurrently. Consider the increased falls risk resulting from anticholinergic adverse effects (e.g. drowsiness, mydriasis).
- Patients with high ACB as this impacts negatively on a range of long term outcomes, including cognitive and physical impairment, hospital admissions and mortality.

AGAINST DEPRESCRIBING

- Depreschribing anticholinergics medicines may not be appropriate in certain scenarios.[25] For example:
  - Antipsychotics when prescribed for schizophrenia, bipolar disorder or severe BPSD (e.g. violent aggression).
  - TCAs for severe and/or recurrent depression or neuropathic pain.
  - SSRIs and SNRIs when prescribed for severe and/or recurrent depression or other psychiatric conditions (e.g. obsessive compulsive disorder, generalized anxiety disorder).
  - Benzodiazepines for severe anxiety or grief, alcohol withdrawal or acute insomnia.
  - Oxybutynin when prescribed for urinary incontinence when symptoms are improving, and adverse effects are either not apparent or not significantly affecting the patient, and/or where other treatment options are ineffective or inappropriate.
  - Antihistamines for allergic conditions requiring ongoing treatment where other options have failed.
- In cases where patients are taking anticholinergic medicines but have a low overall ACB and are not displaying any apparent or significant anticholinergic adverse effects. In such case, continue to monitor and re-assess ACB when new medicines are prescribed.

DISCONTINUATION SYNDROMES

Ceasing anticholinergic medicines abruptly can potentially result in the development of anticholinergic discontinuation syndrome, the severity of which may vary depending on the anticholinergic medicine involved. In general, these withdrawal effects can include nausea, sweating, tachycardia, incontinence, anxiety, orthostatic hypotension and insomnia.[1]

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