https://doi.org/10.33591/sfp.48.5.uo1

ANTICHOLINERGICS IN OLDER ADULTS – AVOID, REPLACE, AND MONITOR

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ABSTRACT

Many medicines have varying degrees of anticholinergic activity. Some of these drugs, particularly those with intermediate or low activity, are not commonly known to possess anticholinergic properties. Regardless of their anticholinergic potency, when used concurrently, they could collectively contribute to the anticholinergic burden in elderly patients. While most of the adverse effects from the anticholinergic burden are reversible upon withdrawal of the anticholinergics, some of the adverse effects on the central nervous system (CNS) may be permanent. Fortunately, for most of the indications for strong anticholinergics, safer alternatives, both non-pharmacological and pharmacological, are available. Therefore, strong anticholinergics should be avoided, especially in older patients already on multiple drugs with anticholinergic activity. This is particularly relevant to those with comorbidities that would put them at risk of the adverse anticholinergic effects. If the use of a drug with strong anticholinergic activity is necessary for an older patient, it should be given at the lowest effective dose for the shortest possible period. Last but not least, the risks and benefits of the drug should be reviewed regularly in a timely manner.

Keywords: anticholinergics, elderly, anticholinergic burden

SFP2022; 48(5):

INTRODUCTION

Evidence of harm stemming from anticholinergics in older persons has increased over the years. Of the 34 classes of drugs specified as generally inappropriate in the older persons in the 2019 American Geriatrics Society (AGS) Beers Criteria, five are listed due to their strong anticholinergic effects.[1-3]

Although there is no direct study of how prevalent such agents are in the community among the elderly in Singapore, this could be a significant public health problem based on anecdotes and indirect evidence.[4]

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Anticholinergics consist of multiple drug classes. Some of these drugs are not used due to their anticholinergic effects. These include drugs such as tricyclic antidepressants (e.g., amitriptyline, imipramine), skeletal muscle relaxants (e.g., orphenadrine in Anarex), first-generation antihistamines (e.g., chlorpheniramine, hydroxyzine, diphenhydramine, promethazine), etc. Examples of drugs used for their anticholinergic effects are antimuscarinics (e.g., oxybutynin, tolterodine, flavoxate) and antiparkinson drugs (e.g., benzhexol). Fortunately, avoiding and replacing most of the drugs are feasible.[5]

This narrative review paper aims to review the latest evidence and mechanisms of harm from anticholinergics and explore the concept of anticholinergic burden and ways to deal with this burden. Alternatives are also suggested to replace the strong anticholinergics for various indications. It is hoped that this paper will help create awareness of the dangers of inappropriate use of strong anticholinergics in the community.

CENTRAL CHOLINERGIC (MUSCARINIC) SYSTEM

The central cholinergic nervous system is integral to cognitive functions such as memory, executive functions, language skills, etc. Its neurotransmitter is acetylcholine. Normal ageing is associated with a decline in the cholinergic nervous system. In the presence of neurodegenerative diseases such as Alzheimer's Disease, further impairment occurs. Hence, there is no surprise that drugs with anticholinergic properties could negatively impact older adults' cognitive and functional capacity. In addition, there is mounting evidence to suggest that the ill effects of anticholinergics on the central nervous system (CNS) may be permanent if the use of such agents is prolonged.[1,2,5,8-10]

NEGATIVE IMPACT OF THE ANTICHOLINERGICS ON CNS MAY BE IRREVERSIBLE

Anticholinergics can cause such CNS-adverse reactions as dizziness, ataxia, fatigue, and drowsiness. They are deemed to be fully reversible upon discontinuation of the offending agents. However, some of the CNS effects may be permanent.

Delirium is a medical emergency that is frequently multifactorial. Anticholinergics invariably feature high on the list of factors that predispose and precipitate delirium in susceptible older adults. In patients with Alzheimer's Disease, the effect of delirium may be long-lasting well after it is resolved in that the rate of cognitive decline could accelerate.[6,7]

On the other hand, prolonged use of anticholinergics may also cause permanent harm in healthy older persons, as multiple studies have pointed to a link between the use of such drugs and an increased risk of dementia. As these studies were observational, a causal relationship cannot be conclusively proven. However, some of these studies demonstrated a dose-dependent relationship between strong anticholinergics exposure and dementia risk. In addition, there are biological rationales for the association. This means that the possibility of a causal relationship between anticholinergics and dementia should be taken seriously. This is more so as most of the conditions for which the drugs are used can be managed without subjecting the patients to increased anticholinergic burden.[1,2,8-10]

PERIPHERAL CHOLINERGIC (MUSCARINIC) SYSTEM

The muscarinic cholinergic receptors are also widely distributed in multiple organs outside the CNS, such as the eyes, mouth, heart, gastrointestinal tracts, bladder, etc. The consequences of blocking the receptors are not a mere nuisance to the geriatric population; they may be severe enough to adversely affect the patients' safety, quality of life, and functional capacity.[5,11]

Effects of Anticholinergics on the Peripheral Cholinergic (Muscarinic) System – More Than Just a Nuisance!

Dry mouth resulting from anticholinergics in younger patients may not be a significant problem. However, an elderly person with the same problem could experience xerostomia-related dysphagia, reduced appetite, or both. In addition, the reduced antibacterial activity from the decreased saliva could worsen oral hygiene and potentially predispose older adults to respiratory infections. In older adults with comorbidities requiring fluid restriction, such as advanced chronic kidney disease or heart failure, this could prove especially challenging to achieve unless the anticholinergic burden is eliminated or reduced.

The muscarinic receptors are found in the lacrimal glands and ciliary muscles in the eyes. Therefore, besides dry eyes, anticholinergics could also cause blurred vision by disrupting the ciliary muscle's functions. This could potentially contribute to the increased risk of falls associated with anticholinergics.

The contraction of the bladder requires activating the muscarinic receptors on the detrusor muscles. Hence, the inhibition of the receptors by the anticholinergics decreases the bladder contraction strength and prevents effective voiding, leading to acute urine retention. This is significantly more likely when conditions causing bladder outlet obstruction are present, e.g., Benign Prostatic Hyperplasia, faecal impaction, urethra stricture, renal stone, concurrent use of alpha-adrenergic agonist (e.g., Midodrine), etc. This urological emergency tends to cause irreversible harm if not promptly treated.

Like many other conditions prevalent among older adults, constipation is multifactorial. The use of anticholinergics is a well-known modifiable risk factor for the problem. Poor bowel habit adversely affects the quality of life and could harm the patients' physical health. In addition to paralytic ileus and decreased nutritional intake, constipation has also been linked to an increased risk of cardiovascular events.[5,11-13]

UNBURDENING THE ANTICHOLINERGIC BURDEN

The anticholinergic burden is the sum of the anticholinergic activities of all the medications taken by a patient. The ability to block the cholinergic receptors in both the CNS and the periphery is possessed by a multitude of drugs. Many of them are not widely recognised as having anticholinergic activities (refer to **Tables 1 and 2**). Most of these agents with "hidden" anticholinergic properties have minimal to moderate anticholinergic activity. Even so, if multiple agents of lesser anticholinergic potency are used concurrently, considerable anticholinergic burden could still result as the inhibitory effects are cumulative. The risk of harm would increase further if strong anticholinergics are added.[5]

The problems posed by the increased anticholinergic burden could be disastrous if it is left unchecked.[11] Clinicians, especially those who serve in the community, have a great responsibility in recognising, eliminating – or at least reducing – and preventing the occurrence of anticholinergic burden.

The most effective way to avoid creating or worsening the anticholinergic burden in an older adult is to stay away from using medications with strong anticholinergic properties (refer to **Table 1**) in the first place. Fortunately, there are safer alternatives to these strong anticholinergics (refer to **Table 1**).[3,14]

It is not uncommon for an older adult to suffer from multiple comorbidities requiring treatment with a multitude of drugs. This invariably increases the chance of older adults being afflicted with a high anticholinergic burden. Many of these patients are cared for by multiple clinicians, who may not fully know the patients' medications. Therefore, at every encounter with an elderly patient in a care setting, presentation with the anticholinergic symptoms of xerostomia, constipation, tachycardia, blurred vision, confusion, sedation, and memory impairment should prompt a review of all the medications consumed by the patient as part of the clinical workup.

Clinicians practising in settings where pharmacists are available may inquire if the latter can help with the medication review. If medications with anticholinergic properties are identified (refer to **Tables 1 and 2**), the need for each medication should be determined. The ones with the most

significant net risk should be prioritised for discontinuation. However, to ensure successful deprescribing, the patients and their caregivers must be actively engaged. The risks and benefits of deprescribing anticholinergics should be discussed. For anticholinergics that have been used daily for weeks to months, especially if the dose is high, gradual withdrawal over a few weeks is advisable. This would help prevent or reduce the severity of anticholinergic withdrawal symptoms such as nausea, vomiting, anxiety, palpitation, dizziness, and headache. The patients should be reassured that these symptoms, if present, are self-limited.[11,15,16] If the indications for which the ceased strong anticholinergics were used are still relevant, they should be treated non-pharmacologically, with safer medications, or both.

Table 1. Examples of Common Oral Drugs with Strong Anticholinergic Effects Registered in Singapore* and alternatives to Strong Anticholinergics

Therapeutic Class	Strong Anticholinergics	Alternatives
First-Generation Antihistamine	Brompheniramine Carbinoxamine (e.g., Became®- with pseudoephedrine) Chlorpheniramine Cyproheptadine Dexchlorpheniramine Dimenhydrinate Diphenhydramine Hydroxyzine Meclizine Promethazine Triprolidine	For allergic rhinitis: • Intranasal Normal saline • Intranasal Corticosteroid (e.g., beclomethasone, fluticasone, mometasone) • Newer less sedating antihistamines (e.g., cetirizine, desloratadine, fexofandine, loratadine) • Leukotriene Receptor Antagonists (e.g., monteleukast) • Intranasal sodium cromoglycate (not registered in Singapore)[14,20] For rhinitis associated with common cold: • Intranasal Normal Saline • Nasal decongestant (e.g., oxymetazoline) not more than 3 days for nasal congestion • Newer antihistamines (e.g., cetirizine, desloratadine, fexofandine, loratadine)[§] • Intranasal sodium cromoglycate (not registered in Singapore)[21-23] For cough associated with common cold/upper respiratory tract infection: • Acetylcysteine/Carbocysteine • Guaifenesin • Dextromethorphan[†] • Oral vitamin C (at least 200 mg/day) (for prevention only)[21,24] For symptomatic relief of itch: • Topical moisturisers/emollients plus other non-pharmacological measures[II] • Judicious use of Topical Corticosteroids for inflammatory dermatoses • Newer less sedating antihistamines • Others: Use gabapentin, pregabalin, mirtazapine, etc judiciously[25]
Antiparkinsonian agents	Benzhexol Benztropine	• Levodopa/carbidopa or benserazide[14]

Antispasmodic	Atropine • (e.g., Lomotil*) Clidinium-chlordiazepoxide Dicyclomine • (e.g., Veragel-DMS*, Acolic* Syrup, Colimix* Syrup, Meclosil* Tablet) Hyoscine Propantheline¶	For relief of GI discomforts associated with AChEI used to treat Myasthenia Gravis: • Mebeverine[26,27]
Antidepressant	Amitriptyline Clomipramine Desipramine Dothiepine Doxepine (>6 mg) Melitracen‡ (Deanxit*, in combination with flupentixol) Imipramine Nortriptyline Paroxetine	For depression: • SSRI (except paroxetine), SNRI, bupropion For neuropathic pain: • SNRI, pregabalin, gabapentin, lignocaine patch, capsaicin topical[14]
Skeletal Muscle Relaxant	OrPhenadrine	For acute mild to moderate pain: • Paracetamol, NSAIDs (judicious use, e.g., no heart failure, eGFR >30 ml/min, use PPI for gastroprotection if used for >7 days)[14]
Antimuscarinics	Flavoxate Oxybutynin Solifenacin Tolterodine Trospium	For Overactive Bladder • Therapy is to improve QOL. Treatment with antimuscarinics may not benefit patients who are unable to perceive positive impact on QOL (e.g., patients with dementia) • Negative impact on cognition may not be obvious to patients. Third-party observation and vigilance are essential (observe and report problems such as functional decline, memory lapses, confusion, etc). • UpToDate recommends non- pharmacological measures (e.g., scheduled voiding) or mirabegron, a Beta 3 receptor agonist, in patients with dementia. Antimuscarinics with theoretically less CNS adverse effects such as trospium, darifenacin, etc have not been studied and proven to be safe in this patient population
Antipsychotics	Chlorpromazine Clozapine Olanzapine Perphenazine Thioridazine Trifluoperazine	For psychosis: • Refer to the respective specialist

* Compiled based on 2019 American Geriatrics Society (AGS) Beers Criteria

† The evidence of efficacy for the mucolytics and dextromethorphan is of poor quality

‡ It is a tricyclic antidepressant as stated in the prescribing information leaflet approved by the Health Science Authority of Singapore

§ Newer less-sedating antihistamines are listed as an alternative because they are associated with lower side effect burden. Their efficacy in common cold is still an issue requiring further research. On the other hand, the sedating antihistamines have been shown to have no clinically significant benefits

[II] Refer to **Table 5** of Ref 25, available from https://www.edf.one/dam/jcr:9c925c23-fa0f-4765-8592-a86a75ce0ec3/GL_Chronic_pruritus.pdf

Mebeverine is suggested as an alternative to propantheline by the Association of British Neurologists for the cholinergic side effects induced by pyridostigmine, an AChEI. Mebeverine is free from anticholinergic side effects

AChEI = Acetylcholinesterase Inhibitor
eGFR = estimated glomerular filtration rate
NSAID = non-steroidal anti-inflammatory drugs
PPI = proton pump inhibitors
QOL = quality of life
SSRI = selective serotonin reuptake inhibitors
SNRI = serotonin-norepinephrine reuptake inhibitors

Table 2. Examples of Oral Medications with Mild to Moderate Anticholinergic Effects Registered in Singapore[18,19]

Moderate Anticholinergics	
Amantadine	
Carbamazepine	
Cetirizine	
Loratadine	
Pethidine	
Mild Anticholinergics	
Alprazolam	Isosorbide
Alverine	Levodopa/Carbidopa
Atenolol	Loperamide
Bupropion	Metoclopramide
Captopril	Metoprolol
Chlorthalidone	Mirtazapine
Cimetidine	Morphine
Codeine	Nifedipine
Colchicine	Pramipexole
Desloratadine	Prednisone
Diazepam	Quetiapine
Digoxin	Quinidine
Dipyridamole	Ranitidine
Entacapone	Risperidone
Fentanyl	Selegiline
Fexofenadine	Theophylline
Fluvoxamine	Trazodone
Frusemide	Triamterene
Haloperidol	Warfarin
Hydralazine	
Hydrocortisone	

WHEN USING STRONG ANTICHOLINERGICS IS DEEMED UNAVOIDABLE

While the use of medications with strong anticholinergic properties should be avoided, especially in patients with significant pre-existing anticholinergic burden, the following measures should be taken in the event such agents are deemed clinically appropriate:

- Review the need for other medications with anticholinergic properties. Deprescribe, i.e., cease or reduce dosage of these medications, if possible, to reduce or eliminate the background anticholinergic burden before initiating the new essential anticholinergic agent. If there is a concern about the occurrence of withdrawal reactions when abruptly ceasing a drug, a good rule of thumb is to tail off the drug at the same rate that it can be safely titrated up.
- Start the strong anticholinergic agent at the lowest possible dose and titrate up the dose cautiously. The risks and benefits of the drug should carefully be assessed at every encounter.
- The patients and their caregivers should be educated about the benefits and risks of the new agent. In addition, a concise action plan, which includes information on what side effects to look out for and when to seek medical attention, should be given.
- Lastly, remember the adage, "Medications that were good then, might not be the best choice now" (cited from https://deprescribing.org). If possible, medications with strong anticholinergic effects should be used, if at all, at the lowest possible dose for the shortest possible period. This is especially relevant now with the knowledge that prolonged exposure to highly anticholinergic drugs may increase the risk of dementia.[17]

Case study:

Mr ABC was an 85-year-old Chinese gentleman who came for Renal follow-up at a hospital. The physician referred him to the pharmacist for medication reconciliation and to review if his medications were contributing to his recent inability to restrict fluid intake. Mr ABC's medications were managed by his spouse at home.

The patient was found to have increased fluid intake around mealtimes. Both the patient and his spouse explained that it was to help him swallow food. Upon further questioning, his spouse shared that he had been complaining of xerostomia for the past few weeks. As a result, he had required more soup and gravy to go with his meals.

Besides his usual chronic medications for CKD, hypertension, heart failure, diabetes mellitus, and hyperlipidaemia, he was also on hydroxyzine 25 mg nightly, which had been started several weeks ago for pruritis. However, according to his spouse, hydroxyzine was ineffective. He also complained of increased drowsiness and occasional constipation.

The patient's spouse also shared that bethanechol was started not long after hydroxyzine was initiated as Mr ABC had refused an indwelling catheter insertion.

The physicians who had started hydroxyzine and bethanechol were contacted and they agreed to stop the medications. However, Mr ABC was required to return for an earlier review of his urinary problem. His spouse was contacted a week later, and she shared that she had stopped giving him hydroxyzine and bethanechol. In addition, she reported that the patient did not have lower limbs oedema that required extra doses of frusemide. He also reported having fewer lower urinary tract symptoms, constipation and sedation.

Hydroxyzine is a first-generation antihistamine commonly used for pruritus. Due to its high burden of side effects, using this class of drugs for pruritis is discouraged.[25] As demonstrated in the above case, the use of strong anticholinergic led to a prescribing cascade involving frusemide and bethanechol, which is a cholinergic agent supposedly meant to help with detrusor muscle contraction. The case underlines the importance of avoiding strong anticholinergics if possible, and if they are used at all, their risks and benefits should be closely reviewed.

CONCLUSION

Muscarinic cholinergic receptors are found both within and without the CNS. Multiple drugs can antagonise the activities of acetylcholine at the receptors. When used concurrently in elderly patients, these drugs create an anticholinergic burden that could result in tremendous morbidity in the patients and negatively impact their quality of life. Over time, more evidence has also become available to show that prolonged exposure to drugs with high anticholinergic properties may increase the risk of dementia. Many indications for which strong anticholinergics are employed can be managed effectively using non-pharmacological measures or safer drugs. In situations where the use of strong anticholinergics cannot be avoided, the patients should be closely monitored for efficacy and safety. Exposure to such medications in the elderly should be as minimal as possible, if at all.

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LEARNING POINTS

- **Many of the commonly used drugs have anticholinergic properties. Although most of them have only mild to moderate anticholinergic activity, when enough of them are used concomitantly, they could result in considerable anticholinergic burden/adverse effects.**
- **As the cholinergic (muscarinic) receptors are present in multiple organ systems, including the central nervous system (CNS), the adverse effects of the anticholinergic burden could result in cognitive impairment and dysfunctions of such organs as the gastrointestinal tract, urinary tract, eye, etc. These may be serious enough to cause deterioration in the quality of life and the functional status, particularly in a frail older patient.**
- **Anticholinergic adverse effects are mostly reversible, but the evidence is accumulating that prolonged exposure to strong anticholinergic drugs may be a risk factor for dementia development. In addition, even brief exposure to anticholinergic drugs could accelerate cognitive decline in patients with pre-existing dementia through the precipitation of delirium.**
- **Strong anticholinergics can and should be avoided in older persons because safer alternatives are available. If treatment with these agents is unavoidable, the therapy should be regularly reviewed. Given that strong anticholinergics may increase the risk of dementia, such agents should be used at the lowest possible dose for the shortest period possible. To minimise the negative impact of the anticholinergic burden, pre-existing but non-essential agents with anticholinergic properties should be ceased.**