We are IntechOpen, the world’s leading publisher of Open Access books Built by scientists, for scientists

5,200
Open access books available

127,000
International authors and editors

150M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected. For more information visit www.intechopen.com
Chapter

Assessing Anticholinergic Effects in Older Adults

Donna M. Lisi

Abstract

Anticholinergic medications are widely used in older adults and are a common source of adverse events in this population. Common drug classes include antiarhythmics, antidepressants, antiemetics, first generation antihistamines, urinary incontinence antimuscarinic agents, antiparkinsonian agents, antipsychotics, antispasmodics, and skeletal muscle relaxants. These drugs have been associated with delirium, cognitive impairment, sedation, dizziness, falls, fracture, constipation, urinary retention, blurred vision, tachycardia and dry mouth. If possible, these drugs should be avoided in older adults or less toxic agents within the class should be utilized. This chapter will explore the mechanism of action of anticholinergic drugs at both the cellular and organ system level; discuss how to assess for anticholinergic drug burden; list medications with anticholinergic effects as identified in the Beer’s criteria on potentially inappropriate medication use in older adults; review anticholinergic drug–drug interactions; describe contraindications to the use of anticholinergic agents; and explore practical considerations such as the availability of these substances in nonprescription medications, their use at end of life and deprescribing.

Keywords: anticholinergic medications, Beer’s criteria, adverse drug events, older adults, geriatrics

1. Introduction

1.1 Anticholinergic agents in nature

1.1.1 Hyoscyamine

1.1.2 Belladonna

Anticholinergic agents are substances that antagonize the effects of acetylcholine, a neurotransmitter formed by an ester of choline and acetic acid, that facilitates nerve impulses in both the central (CNS) and peripheral nervous systems. Acetylcholine is the main neurotransmitter of the parasympathetic system. It is also located within parts of the autonomic nervous system. [1] Anticholinergic agents are present in both pharmaceuticals and in nature. Substances like hyoscyamine and belladonna are naturally occurring anticholinergics which have been used medicinally to control gastric secretions, for irritable bowel symptoms, and for urinary spasms. [2] However, despite their natural origins, the use of these drugs is not without consequence and should be avoided in older adults.
2. Anticholinergics physiological effects

2.1 Mechanisms of action

2.1.1 Cellular effects

2.1.2 Organ system involvement

2.1.2.1. Brain

2.1.2.2. Eyes

2.1.2.3. Glands (salivary, sweat)

2.1.2.4. Heart

2.1.2.5. Lungs

2.1.2.6. Gastrointestinal tract

2.1.2.7. Bladder/genitourinary system

2.1.2.8. Skin

The cholinergic receptors are divided into muscarinic receptors or nicotinic receptors. There are five subtypes of muscarinic receptors, M1-M5 and two types of nicotinic receptors, N\textsubscript{M} (skeletal muscle) and N\textsubscript{n} (neuronal). M1 are found in the CNS (i.e., the cerebral cortex, hippocampus, striatum and thalamus), autonomic ganglia, gastric and salivary glands and the enteric nerves of the GI tract. M2 are located in the CNS (i.e., the hindbrain, thalamus, cerebral cortex, hippocampus, striatum, heart, smooth muscle, and autonomic nerve terminals). M3 receptors have less of a presence in the CNS although they are found in the cerebral cortex and hippocampus. They are abundant in smooth muscle and glands and the heart. M4 is preferentially expressed in the CNS (i.e., forebrain, striatum, cerebral cortex and hippocampus) while M5 are only expressed in low levels in the CNS and periphery and are found primarily in the substantia nigra and ventral tegmentum area. N\textsubscript{M} are located at the neuromuscular junction and are involved in muscle contraction. N\textsubscript{n} are found in the autonomic ganglia and adrenal medulla. [3]

At the cellular level, anticholinergic agents act by opposing the effects of acetylcholine either at the muscarinic or nicotinic receptors. In the geriatric population, most anticholinergic drugs affect the muscarinic receptors. On the organ system level, these compounds have varying effects. Although some effects are therapeutic, it’s their toxic effects that are most worrisome, especially in geriatric patients.

While M1-M5 receptors are found in the brain, most of the deleterious effects on the CNS come from antagonizing M1 receptors. This can lead to delirium, cognitive impairment, dizziness, sedation and confusion. The predominant form of muscarinic receptors in the eyes are M3 although M1-M5 receptors are also present. Blocking these receptors leads to mydriasis and blurred vision. It is for this reason that ophthalmic atropine, a potent anticholinergic agent, is used to produce pupillary dilation and/or cycloplegia. Blocking of M1 and M3 receptors in salivary glands leads to dry mouth and difficulty swallowing whereas opposing the effects of M3 receptors in sweat glands leads to the inability to dissipate heat and can result in overheating, especially during the warmer months. The heart is primarily composed
of M2 receptors and antagonizing these receptors leads to sinus tachycardia and increased contractility. Systemic atropine is used in the management of symptomatic sinus bradycardia and atrioventricular nodal block. The lungs primarily contain M1-M4 receptors and blocking these receptors results in bronchodilation. The use of long- and short-acting inhalation antimuscarinic agents in chronic obstructive pulmonary disease (COPD) takes advantage of this beneficial effect. Opposing M2 and M3 receptors in the GI tract can lead to gastric stasis and constipation. On the other hand, dicyclomine is an anticholinergic drug that is used for abdominal pain associated with irritable bowel syndrome. Antagonism of M3 receptors in the bladder inhibits detrusor and bladder contractions and is used therapeutically for urinary incontinence. This blockade can also lead to urinary retention. The role of cholinergic agents in the skin, which contains primarily M3 receptors, is complex resulting in increased nitric oxide production and vasodilation and it also involves interplay with nicotinic receptors. [4]

Nicotinic agents act either as neuromuscular blockers (i.e., atracurium, vecuronium, tubocurarine, pancuronium) or ganglionic blockers (i.e., mecamylamine). Succinylcholine is a N\textsubscript{M} receptor agonist. [4]

3.3 Assessment of anticholinergic burden

3.1 Tune

3.2 Anticholinergic cognitive burden scale

3.3 Anticholinergic risk scale

3.4 Drug burden index

The effects of anticholinergic agents are cumulative and there are various tools available to help evaluate the degree of ‘cholinergic burden’ in an older adult’s drug regimen. Early work by Tune et al. resulted in the development of the serum anticholinergic assay, a biologic measure intended to quantify anticholinergic drug burden. [5] Using this assay, it has been shown that many drugs taken by older adults have high serum anticholinergic activity Table 1 [6].

Over 600 medications have some degree of anticholinergic activity. [7] One drawback of using the serum anticholinergic assay is that it may not be readily available in clinical settings and even if available, there can be a delay in care pending interpretation of results. [8]

As a result of these limitations, scales have been developed to easily calculate the cumulative anticholinergic burden. The Anticholinergic Cognitive Burden Scale (ACBS) rates drugs on a scale of 0 (no anticholinergic effect) to 3 with 1 representing a possible anticholinergic effect based on laboratory tests but no evidence of clinically relevant cognitive effects and scores of 2 or 3 indicating definite anticholinergic effects. Higher scores indicate greater anticholinergic burden and warrant a re-evaluation of the drug regimen. The presence of a drug scoring 2 or 3 can increase the risk of cognitive impairment by 46% over 6 years. Further, each point increase in the ACBS has been associated with a decrease in the Mini-Mental Examination Score of 0.33 points over the course of 2 years. This point increase has also been associated with a 26% increase in the risk of death. [9]

Another tool is the Anticholinergic Risk Scale (ARS). Similar to ACBS, the ARS is also a 3-point scale. The developers of the scale assessed whether the ARS could predict the risk of anticholinergic adverse effects in a geriatric evaluation and
Geriatrics

The investigators found that in the GEM group, older adults experienced more adverse CNS effects whereas in the PC group, more elderly had peripheral adverse effects. [10]

The Anticholinergic Drug Scale (ADS), which was previously known as the Clinician-Rated Anticholinergic Scale, is another 3-point scale. It includes the largest number of anticholinergic agents. A score of 0 indicates no known anticholinergic properties; a score of 1 means that the drug has the potential for anticholinergic activity as evidenced by receptor binding sites; a score of 2 represents a drug that causes anticholinergic adverse effects at higher doses; and a score of 3 represents a drug with marked anticholinergic activity. [11]

The Anticholinergic Burden Classification (ABC) measures serum anticholinergic activity but takes into account the duration of exposure, adjusts for mode of administration (i.e., topical, nasal, oral, etc.), assesses for possible drug–drug interactions and for the ability of drugs to cross the blood brain barrier. [12]

The Anticholinergic Activity Scale (AAS) is based on in vivo radioreceptor assay determinations and ranks drugs on five levels: 0 (no anticholinergic activity); 0/+ (no or minimal anticholinergic activity); + (low anticholinergic activity), ++ (moderate anticholinergic activity), and +++ (high anticholinergic activity). [13]

The Anticholinergic Loading Scale (ALS) is a tool used in the Australian Imaging, Biomarkers and Lifestyle (AIBL) study that calculates anticholinergic load. Anticholinergic load was found to have an adverse effect on psychomotor speed and executive function in healthy controls. [14]

The Anticholinergic Effect on Cognition Scale (AECS) is another 3-point scale that uses in vitro anticholinergic potency as well as a drug’s ability to cross the blood brain barrier. [15]

Unlike the previous scales, which only focus on the anticholinergic potential of a drug regimen, the Drug Burden Index (DBI) takes into account anticholinergic effects, sedative effects of medications, and the total number of medications. It measures the effect of cumulative exposure to both anticholinergic and sedative medications on physical and cognitive function in older adults. This scale is based on the minimum recommended daily doses of each drug. Drugs that have both anticholinergic and sedative properties are classified based on their anticholinergic effects. [16] The developers studied this scale in over 3000 healthy

| Medications       | Anticholinergic Drug Level (ng/mL Atropine) |
|-------------------|---------------------------------------------|
| Cimetidine        | 0.86                                        |
| Prednisolone      | 0.55                                        |
| Theophylline      | 0.44                                        |
| Digoxin           | 0.25                                        |
| Furosemide        | 0.22                                        |
| Nifedipine        | 0.22                                        |
| Ranitidine        | 0.22                                        |
| Isosorbide dinitrate | 0.15                                    |
| Warfarin          | 0.12                                        |
| Codeine           | 0.11                                        |
| Triamterene/HCTZ  | 0.08                                        |
| Captopril         | 0.02                                        |

Table 1. Anticholinergic drug level of medications commonly used by older adults.
community-dwelling older adults aged 70–79 years. They found that the use of anticholinergic and sedative medications was associated with poorer physical performance and cognitive performance. Each unit of drug burden on physical function was equal to having three additional physical comorbidities whereas each unit of drug burden on cognition was similar to having four additional physical comorbidities or about half of the effects of anxiety, depression or cognitive impairment. [17]

A recent publication compared several of the anticholinergic scales providing a description of the tool and listing the number of drugs with anticholinergic activity that are included in the scale. [18] However, while many of these scales have shown a significant correlation between anticholinergic burden assessment and serum anticholinergic drug levels, they have limitations. There is currently no ‘gold standard’ to identify an anticholinergic drug. Only parent compounds are included in these scales, therefore, there is no information on active metabolites that may also contribute to the anticholinergic burden. While some scales do take dose into the account, this is not consistently done in all tools. These scales also assume that there is a linear relationship between anticholinergic levels and toxicity. Lastly, serum anticholinergic activity assays do not distinguish between agonist versus antagonist binding of the cholinergic receptors. [19]

4. Medication classes with anticholinergic effects- the Beer’s list of potentially inappropriate medications in older adults

4.1 Antiarrhythmics
4.2 Antidepressants
4.3 Antiemetics
4.4 First generation antihistamines
4.5 Urinary incontinence antimuscarinics
4.6 Antiparkinsonian agents
4.7 Antipsychotics
4.8 Antispasmodics
4.9 Skeletal muscle relaxants

In 1991, Dr. Mark Beers published explicit criteria for the use of ‘potentially inappropriate medications’ or PIMS in older nursing home residents. [20] The Beer’s criteria, which were developed using a two-stage Delphi survey, defined inappropriate prescribing as the use of a medication where the potential risks outweigh the potential benefits. These initial criteria included 30 therapeutic classes/medications that should be avoided in elderly nursing home residents. [21] This list is updated every 3 years by the American Geriatrics Society. At the time of this writing, the latest Beer’s List was published in 2019. The criteria identifies PIMs, drugs that may be PIMS because they may exacerbate disease states or geriatric syndromes, drugs that should be used with caution, drugs that should be avoided, drugs that should be used in reduced doses (if at all) based on renal function, and drugs with strong anticholinergic properties Table 2 [22].
5. Adverse effects of anticholinergics (“Alice in Wonderland”)

5.1 Drowsiness/sedation

5.2 Cognitive impairment/confusion/delirium/hallucinations

5.3 Blurred vision

5.4 Dizziness

5.5 Falls/fracture

5.6 Urinary retention

5.7 Constipation

5.8 Tachycardia

5.9 Xerostomia

5.10 Use of anticholinergic PIMs in older adults with dementia and delirium

5.11 Use of anticholinergic PIMS in older adults resulting in falls/fracture

5.12 Use of anticholinergic PIMs in older adults and mortality

As mentioned previously, cholinergic receptors are found in various organ systems throughout the body. Blocking these receptors can have both therapeutic
Assessing Anticholinergic Effects in Older Adults
DOI: http://dx.doi.org/10.5772/intechopen.94555

and toxic effects. The mnemonic “red as a beet, dry as a bone, blind as a bat, mad as a hatter, hot as a hare, full as a flask” reflects the classic signs and symptoms of anticholinergic poisoning. [23] However, adverse events in older adults may be more subtle. These can include drowsiness, sedation, cognitive impairment, confusion, delirium, hallucinations, blurred vision, dizziness, falls/fractures, urinary retention, constipation, tachycardia, and xerostomia. [3, 22].

Adverse CNS effects can be particularly burdensome among older adults. A recent study examining the effects of PIMs in patients with dementia found that almost one-quarter of adults aged ≥65 with cognitive impairment used drugs with clinically significant anticholinergic effects. This study measured anticholinergic burden using the ADS. [11] It found that the level 2 drugs that were most prescribed were ranitidine and cyclobenzaprine and the most commonly prescribed level 3 drugs were meclizine, tolterodine and oxybutynin. [24] A systematic review examining drug-induced delirium found that ARS scores were consistently associated with delirium. [25] A recent retrospective analysis found that if older hospitalized adults scored 3 or higher on the ACBS, they had a 3–6 fold increased risk of developing delirium compared to those who score <3 on this tool. [26] In older adults with mild to moderate Alzheimer’s disease who were APOE-ε4 carriers, there was a positive correlation between greater progression of dementia severity and continued use of anticholinergic medications. [27]

In addition to the CNS effects of anticholinergic agents in older adults, another concern is the risk of falls and fracture. After following women with a mean age of 55 years for approximately 24 months, the APOS (Aberdeen Prospective Osteoporosis Screening Study) found that those with an ACB of ≥2 had a 2.34-fold increased odds of having had recurrent falls in ‘later life’ with ‘later life’ referring to 12 months prior to follow-up; there was a 2-year follow-up period. They postulated that anticholinergic agents may contribute to falls by causing vision problems secondary to pupillary dilation, dizziness, slowed reflexes and/or cognitive impairment. [28]

Death, the most significant anticholinergic adverse event, was observed in a systematic review of studies examining the association between anticholinergic burden and mortality in older adults. Of the 27 studies included in this systematic review, 63% of studies found a positive relationship between anticholinergic drug burden and mortality in older adults. When solely analyzing those studies that were deemed to be of the highest quality, the association between anticholinergic drug use and death rose to 80% in the elderly. [29]

6. Drug interactions involving anticholinergic agents

6.1 Acetylcholinesterase inhibitors

6.2 Potassium

6.3 Carbonic anhydrase inhibitors

6.4 Opioids

6.5 Other “moderate” anticholinergic drug-drug interactions

Besides the anticholinergic drug–drug interactions that lead to an increased anticholinergic burden, anticholinergic agents are involved in other potential drug–drug interactions.
The use of an anticholinergic agent with an acetylcholinesterase inhibitor (i.e., donepezil, galantamine and rivastigmine) results in opposing pharmacodynamic effects and can negate any small, positive benefits seen with the Alzheimer’s disease agents. [30] Conversely, acetylcholinesterase inhibitors have the potential to interfere with the therapeutic effects of anticholinergic agents. Concomitant use is not recommended. [31–33]

The concomitant administration of an anticholinergic agent and an oral solid dosage form of potassium supplement can increase the risk of GI bleeding. A liquid formulation of potassium supplement should be utilized instead if concurrent therapy is required. [34–36]

Anticholinergic agents also interact with carbonic anhydrase inhibitors such as topiramate and zonisamide potentiating the risk of oligohidrosis and hyperthermia. Patients should be monitored for decreased sweating and increases in body temperature. These combinations should be avoided. [37, 38]

Concurrent use of opioids and anticholinergics can lead to severe constipation (resulting in paralytic ileus), sedation, dizziness, confusion, cognitive and psychomotor impairment, dry mouth and urinary retention. Caution is advised. [39]

‘Moderate’ (i.e., drug–drug interactions for which combination therapy should be avoided or used only under special circumstances) anticholinergic drug–drug interactions include abobotulinumtoxin A, acetbutolol, acetylcholine ophthalmic, aclidinium, acrivastine, alfentanil, aluminum hydroxide, amantadine, ambenonium, amitriptyline, amoxapine, arbutamine, aripiprazole, asenapine, atenolol, azatadine, belladonna, benzotropine, betaxolol, betanechol, biperiden, bisoprolol, brexanolone, brexiprazole, brompheniramine, busprenorphine, butorphanol, calcium carbonate, carbachol ophthalmic, carboinoxamine, cariprazine, carteolol, carvedilol, clemastine, clidinium, clomipramine, clozapine, cyclizine, cyclobenzaprine, cyproheptadine, darifenacin, demecarium bromide ophthalmic, desipramine, dexbrompheniramine, dexchlorpheniramine, dezocine, dicylecine, dimenhydrinate, diphenhydramine, disopyramide, doxepin, doxylamine, ephedrine, ethosuximide, ethylnitrite, ethambutol, ethanol, eseretidine, flavoxate, flubenzamine, fluphenazine, glycopyrrolate, glycopyrronium topical, guanidine, haloperidol, hydroxyzine, hyoscyamine, iloperidone, imipramine, incobotulinumtoxin A, ipratropium, isoflurophate ophthalmic, kaolin, ketoconazole, labetalol, lasmiditan, levodopa, loperamide, loxapine, lumateperone, lurasidone, macimorelin, magaldrate, magnesium carbonate, magnesium hydroxide, maprotiline, meclizine, memantine, meprenzolate, mesoridazine, methadiazine, methotrimazone, methsulphaphenylone, metoclopramide, metoprolol, molindone, nadolol, nalbuphine, nebivolol, neostigmine, noralpazine, olanzapine, olopatadine nasal, onabotulinumtoxin A, orphenadrine, oxybutynin, paliperidone, penbutolol, perphenazine, phenindamine, phenergan, phycodazone, phensistigmine, pilocarpine, pimozone, pindolol, prabotulinumtoxin A, pramlintide, procacid, procyclidine, promazine, promethazine, propantheline, propacetamol, propranolol, protriptyline, prucalopride, pyridostigmine, pyrilamine, quetiapine, quinapril, remifentanil, revafenacine, rimabotulinumtoxin B, risperidone, scopolamine, sodium bicarbonate, solifenacin, sotalol, sufentanil, thalidomide, thioridazine, thiothixene, timolol, tiotropium, tizanidine, tolterodine, trifluoperazine, triflupromazine, trihexyphenidyl, trimeprazine, trimipramine, triprolidine, trosquip, umeclidinium and ziprasidone. [40]
7. Contraindications to the use of anticholinergic agents

7.1 Narrow angle glaucoma

Anticholinergic agents cause pupillary dilation, which is detrimental in patients with narrow angle or primary angle closure glaucoma. When the pupils dilate, this increases pressure within the eye. This increase in pressure prevents drainage of aqueous humor from the eye resulting in marked increases in ocular pressure and acute pain. If left untreated, this can lead to optic nerve damage and vision loss. The use of anticholinergics is contraindicated in patients with this type of glaucoma [41].

7.2 Obstructive uropathy

In overactive bladder, there are excessive contractions of the detrusor muscle producing incomplete emptying of the bladder. By blocking M3 receptors in the genitourinary tract, this causes smooth muscle relaxation and detrusor underactivity, which can lead to urinary retention. In the presence of benign prostate hyperplasia, there is compression of the urethra, which blocks the flow of urine. Anticholinergic agents are contraindicated in patients with urinary retention and bladder neck obstruction caused by prostatic hypertrophy since the use of these agents can result in an increased risk of developing an obstructive uropathy. [42]

7.3 Myasthenia gravis

Myasthenia gravis is an autoimmune disorder of the postsynaptic neuromuscular junction caused by antibody-mediated blockade of neuromuscular transmission that results in skeletal muscle weakness. Autoimmune antibodies form at the neuromuscular junction against nicotinic acetylcholine postsynaptic receptors. Anticholinergics, especially agents that block nicotinic cholinergic receptors, are contraindicated because they exacerbate muscle weakness. Further, acetylcholine esterase inhibitors such as pyridostigmine are considered the mainstay of treatment. The use of anticholinergic agents would antagonize the effects of these drugs. [42, 43]

7.4 Obstructive gastrointestinal tract disease

Anticholinergic agents block M1 and M2 receptors in the GI tract, which results in slowed GI motility. Ogilvie’s syndrome or colonic pseudo-obstruction, which is massive dilation of the colon without underlying mechanical obstruction or other organic causes, can be due to the use of anticholinergic agents. These drugs can lead to an adynamic colon. Anticholinergic drugs are contraindicated in patients with achalasia, esophageal stricture or stenosis, pyloroduodenal stenosing peptic ulcer disease, pyloric obstruction and paralytic ileus. [42, 44]

Stimulation of M2 receptors in the heart slow pacemaker activity and atrioventricular (AV) conduction, which decreases contractility. Blocking these receptors leads to sinus tachycardia and increased oxygen demand. [45] Analyses of data from the EPIC (European Prospective Investigation into Cancer) - Norfolk Population Study, which was a longitudinal, observation, community cohort study, found that among the 21,000 study participants there was an increase in total anticholinergic burden and subsequent risk of all-cause mortality and incident cardiovascular disease during the follow up period. ACBS scores of ≥3 were associated with a hazard ratio of 2.17 (p < 0.00001) for cardiovascular disease incidence and higher
mortality. It was thought that this was a dose-dependent, class effect for the anti-
cholinergic agents. Potential mechanisms of this effect could be a pro-arrhythmic
or pro-ischemic effect, increased hemodynamic lability, cardiac ischemia, cardiac
dysrhythmias in the presence of ischemia, decrease heart rate variability, or an
inflammatory response resulting in an increased risk of mortality. [46] Studies of
the effects of inhalation antimuscarinics on cardiovascular status have been mixed.
[47] Inhalation anticholinergic agents used in chronic obstructive pulmonary
disease have been found to aggravate the balance of the autonomic nervous system
leading to significantly reduced heart rate recovery following maximal cardiopul-
monary exercise. [48] In a longitudinal study of over 3700 nursing home residents
with coronary artery disease, the use of anticholinergics was associated with an
increased risk of hospitalization and all-cause mortality (hazard ratio 1.71 if the
ACB score $\geq 2$). [49] Further, the use of antimuscarinics for urinary incontinence
may also be associated with drug-dependent cardiovascular risk. Among these
agents, darifenacin has not been associated with an increase in heart rate or QT
prolongation because it is M3 selective and it appears to have the best cardiovascular
safety profile. Tropsium, on the other hand, may have the highest risk of adverse
cardiovascular events. On the basis of these drugs’ physiological effects and clinical
trials showing increased cardiovascular risk associated with their use, it is best to
avoid anticholinergics during the post-myocardial infarction period. [50]

8. Practical considerations for the use of anticholinergic agents in older
agents

8.1 Nonprescription drug availability

8.2 End-of-life

8.3 Deprescribing

Anticholinergic medications are readily available over-the-counter. First gen-
eration antihistamines are available as single ingredients or in multiple symptom
cough and cold products. Anticholinergics are marketed as over-the-counter sleep
aids and for urinary incontinence. [51–54] A recent study examining older adults’
medication decision making and behavior in regards to the use of anticholinergic
over-the-counter medications found that while seniors were concerned about
adverse drug events, they were not aware of age-related risk associated with the use
of anticholinergic medications. [55]

Anticholinergic agents are used at end-of-life (EOL) for relief of nausea in those
with a vestibular component and more commonly, to provide symptomatic relief of
excessive secretions. However, data is lacking to support the use of these drugs for
this latter indication. [56, 57]

Given the poor risk versus benefit of anticholinergics in older adults, there has
been a movement to deprescribe these medications in the elderly. The DEFEAT-
polypharmacy was a deprescribing feasibility trial conducted among 46 residential
care residents in New Zealand that targeted the use of anticholinergic and sedative
medications in older adults. Utilizing peer-reviewed deprescribing guidelines and
a collaborative pharmacist-led medication review approach, investigators were
able to demonstrate a 0.34 decrease in DBI scores at 6 months. The total number of
medications were reduced by 2.13 medications per patient. There was a statistically
significant reduction in the number of falls in the past 90 days. There was also a
significant improvement in frailty scores. A significant decline was also observed
Assessing Anticholinergic Effects in Older Adults
DOI: http://dx.doi.org/10.5772/intechopen.94555

in psychiatric, neurological, autonomic and other adverse events with a decrease in psychiatric adverse events of 1.8 three months after deprescribing and increasing to 2.24 after 6 months; other potential adverse events fell by 2.8 at the end of three months and 4.24 at 6 months post initiation of the deprescribing intervention. Participants also reported lower depression scores after six months. Cognition and quality of life were unchanged. [58]

Unfortunately, anticholinergics are sometimes prescribed as part of the prescribing cascade to manage urinary incontinence associated with the use of acetylcholinesterase inhibitors. A population-based retrospective cohort study of 44,884 older adults with dementia conducted in Canada found that there was an increased risk (adjusted hazard ratio 1.55) of subsequently receiving an anticholinergic agent following the initiation of acetylcholinesterase inhibitors. [59] The Choosing Wisely campaign, an initiative of the American Board of Internal Medicine Foundation, is designed to promote conversations between clinicians and patients by helping patients choose care that is supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Dialog has started about the use of anticholinergic agents in older adults. In June 2016, the American Academy of Nursing made the following recommendation: “Don’t administer “prn” (i.e., as needed) sedative, antipsychotic or hypnotic medications to prevent and/or treat delirium without first assessing for, removing and treating the underlying causes of delirium and using nonpharmacologic delirium prevention and treatment approaches”. Anticholinergics are clearly identified as deliriogenic medications. [60]

In June 2020, the American Urogynecologic Society (AUS) issued a recommendation stating to “avoid using anticholinergic medication to treat overactive bladder in women older than 70”. This recommendation was based on the AUS’s concern over the ability of anticholinergic drugs to impair cognition, increase the risk of developing dementia and cause drowsiness and constipation, all potentially detrimental adverse effects in older adults. [61]

9. Conclusions

Cholinergic receptors are found throughout the body, but most especially in the CNS. Substances that block these receptors are available both naturally and pharmaceutically. Depending on the location of cholinergic receptors and their subtype, use of anticholinergic medications can result in adverse drug effects in the CNS, the eyes, the exocrine glands, the heart, the GI tract and genitourinary systems and in the skin. Older adults are especially prone to developing adverse drug events from the use of anticholinergics. Easy to use scales are available to assess the burden of anticholinergic agents in the drug regimen. The Beer’s List includes drugs that are potentially inappropriate for use in older adults because of their strong anticholinergic properties. Adverse events associated with the use of anticholinergic agents include drowsiness, sedation, cognitive impairment, confusion, delirium, hallucinations, blurred vision, dizziness, falls/fractures, urinary retention, constipation, tachycardia and xerostomia. Anticholinergic drugs have also been associated with an increase in mortality. These agents are involved with numerous drug–drug interactions adding to the anticholinergic burden. They can antagonize the effects of acetylcholinesterase inhibitors, contribute to the development of GI bleeding in patients on oral, solid forms of potassium supplementation and lead to hyperthermia in patients concomitantly receiving a carbonic anhydrase inhibitor. Anticholinergics should not be used by older adults, especially those with narrow angle glaucoma, obstructive uropathy, myasthenia gravis, obstructive GI
tract disease and myocardial ischemia. Avoiding prescribing these agents whenever possible is the first step. If they are utilized, it is important for health care professionals to use the lowest doses possible, closely monitor for signs and symptoms of anticholinergic adverse events and to deprescribe as tolerated.

Conflict of interest

The author declares no conflict of interest.

Author details

Donna M. Lisi
PharmD, BCPS, BCGP, BCPP, BCACP, Hackensack Meridian Health, Eatontown, NJ, USA

*Address all correspondence to: drdonnalisi@gmail.com
References

[1] The Editors of Encyclopaedia Britannica. Acetylcholine. Encyclopædia Britannica, Inc. May 12, 2020. Available from: https://www.britannica.com/science/acetylcholine. Accessed 8/15/20.

[2] Rajput H. Effects of Atropa belladonna as an anti-cholinergic. *Natural Products Chem Research*. 2014, 1, 1-2. Available from: https://www.longdom.org/open-access/effects-of-atropa-belladonna-as-an-anti-cholinergic-2329-6836.1000104.pdf. Accessed 6/15/20.

[3] Westfall TC, Macarthur H, Westfall DP. Chapter 8. Neurotransmission: the autonomic and somatic motor nervous systems. In: Brunton LL, Hilal-Dandan R, Knollmann BC, editors. *Goodman and Gilman’s The Pharmacological Basis of Therapeutics*. 13th edition. New York; McGraw Hill; 2018. p. 115-47.

[4] Migirov A, Datta AR. Physiology, Anticholinergic reaction. [Updated 2019 Sep 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546589/. Accessed 6/20/20.

[5] Tune L, Coyle JT. Serum levels of anticholinergic drugs in treatment of acute extrapyramidal side effects. Arch Gen Psychiatry. 1980;37(3):293-297. doi:10.1001/archpsyc.1980.01780160063007

[6] Tune L, Carr S, Hoag E, Cooper T. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry. 1992;149(10):1393-1394. doi:10.1176/ajp.149.10.1393

[7] Ghossein N, Kang M, Lakhkar AD. Anticholinergic medications. [Updated 2020 May 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555893/. Accessed 6/15/20.

[8] Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The Anticholinergic Risk Scale and anticholinergic adverse effects in older persons. *Arch Intern Med*. 2008;168(5):508-513. doi:10.1001/archinternmed.2007.106

[9] National Health Service (NHS) Milton Keynes Clinical Commissioning Group. Anticholinergic Cognitive Burden Scale. Available from: http://www.miltonkeynesc cg.nhs.uk/resources/uploads/ACB_scale_-_legal_size.pdf. Accessed 8/1/20.

[10] Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med*. 2008;168(5):508-513. doi:10.1001/archinternmed.2007.106

[11] Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol*. 2006;46(12):1481-1486. doi:10.1177/0091270006292126

[12] Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ*. 2006;332(7539):455-459. doi:10.1136/bmj.38740.439664.DE

[13] Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. *J Neurol Neurosurg Psychiatry*. 2010;81(2):160-165. doi:10.1136/jn np.2009.186239
Sittironnarit G, Ames D, Bush AI, et al. Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study. Dement Geriatr Cogn Disord. 2011;31(3):173-178. doi:10.1159/000325171

Bishara D, Harwood D, Sauer J, Taylor DM. Anticholinergic effect on cognition (AEC) of drugs commonly used in older people. Int J Geriatr Psychiatry. 2017;32(6):650-656. doi:10.1002/gps.4507

Kouladjian L, Gnjidic D, Chen TF, Mangoni AA, Hilmer SN. Drug Burden Index in older adults: theoretical and practical issues. Clin Interv Aging. 2014;9:1503-1515. Published 2014 Sep 9. doi:10.2147/CIA.S66660

Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med. 2007;167(8):781-787. doi:10.1001/archinte.1678.781

Salahudeen MS, Duffull SB, Nishhtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatr. 2015;15:31. Published 2015 Mar 25. doi:10.1186/s12877-015-0029-9 Available from: https://bmgeriatr.biomedcentral.com/track/pdf/10.1186/s12877-015-0029-9 Accessed 6/15/20

Tune LE. Perspective: Serum anticholinergic drug level determinations after 30 Years. Am J Geriatr Psychiatry. 2016;24(12):1189-1190. doi:10.1016/j.jagp.2016.08.021

Beers MH, Ouslander JG, Rollinger I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. Arch Intern Med. 1991;151(9):1825-1832.

Markum ZA, Hanlon JT. Commentary on the new American Geriatric Society Beers criteria for potentially inappropriate medication use in older adults. Am J Geriatr Pharmacother. 2012;10(2):151-159. doi:10.1016/j.amjpharm.2012.03.002

By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019;67(4):674-694. doi:10.1111/jgs.15767

Broderick ED, Metheny H, Crosby B. Anticholinergic toxicity. [Updated 2020 Jun 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534798/ Accessed 6/15/20.

Sura SD, Carnahan RM, Chen H, Aparasu RR. Prevalence and determinants of anticholinergic medication use in elderly dementia patients. Drugs Aging. 2013;30(10):837-844. doi:10.1007/s40266-013-0104-x

Egberts A, Moreno-Gonzalez R, Alan H, et al. Anticholinergic drug burden and delirium: a systematic review. J Am Med Direct Ass. 2020. Available from: https://doi.org.10.1016/j.jamda.2020.04.019 Accessed 8/1/20

Pasina L, Colzani L, Cortesi L, et al. Relation between delirium and Anticholinergic Drug Burden in a cohort of hospitalized older patients: an observational study. Drugs Aging. 2019;36(1):85-91. doi:10.1007/s40266-018-0612-9

Dyer AH, Murphy C, Segurado R, et al. for the NILVAD Study Group. Is ongoing anticholinergic burden associated with greater cognitive decline and dementia severity in mild
Assessing Anticholinergic Effects in Older Adults
DOI: http://dx.doi.org/10.5772/intechopen.94555

to moderate Alzheimer’s disease?.
J Gerontol A Biol Sci Med Sci.
2020;75(5):987-994. doi:10.1093/gerona/ glz244

[28] Neal SR, Wood AD, Ablett AD, et al. Anticholinergic burden in middle-aged women and recurrent falls in later life: findings from the Aberdeen prospective osteoporosis screening study (APOSS). Ther Adv Drug Saf. 2020;11:2042098620929852.
Published 2020 May 27.
doi:10.1177/2042098620929852
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273562/pdf/10.1177_2042098620929852.pdf
Accessed 6/20/20

[29] Ali, S., Peterson, G.M., Bereznicki, L.R. et al. Association between anticholinergic drug burden and mortality in older people: a systematic review. Eur J Clin Pharmacol. 2020;76: 319-335. Available from: https://doi.org/10.1007/s00228-019-02795-x
Accessed 6/20/20

[30] Horn JP, Hansten P. Cholinergic-anticholinergic drug interactions. Pharm Times. 2005; 71(8): 46.

[31] Donepezil (Aricept®) Prescribing Information. Woodcliff Lakes, NJ; Eisai Pharmaceutical. December 2018.

[32] Galantamine (Razadyne®) Prescribing Information. Titusville, NJ; Janssen Pharmaceutical. March 2020.

[33] Rivastigmine (Exelon®) Prescribing Information. East Hanover, NJ; Novartis Pharmaceutical. December 2018.

[34] Atropine and potassium chloride. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/drug-interactions/atropine-with-potassium-chloride-280-0-1912-0.html?professional=1 Accessed 8/15/20

[35] Atropine and potassium citrate. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/drug-interactions/atropine-with-potassium-citrate-280-0-1914-0.html?professional=1 Accessed 8/15/20

[36] Zarowitz BJ. Oral solid potassium chloride and anticholinergic medications: a new drug interaction for an old drug?. Geriatr Nurs. 2006;27(6):329-333. doi:10.1016/j.gerinurse.2006.10.015

[37] Atropine and topiramate. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/drug-interactions/atropine-with-topiramate-280-0-2216-0.html?professional=1 Accessed 8/15/20

[38] Atropine and zonisamide. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/drug-interactions/atropine-with-zonisamide-280-0-2334-0.html?professional=1 Accessed 8/15/20

[39] Atropine and morphine. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/drug-interactions/atropine-with-morphine-280-0-1656-0.html?professional=1 Accessed 8/15/20

[40] Atropine drug interactions. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/drug-interactions/atropine-index.html?filter=2 Accessed 8/15/20

[41] Wu A, Khawaja AP, Pasquale LR, Stein JD. A review of systemic medications that may modulate the risk of glaucoma. Eye (Lond). 2020;34(1):12-28. doi:10.1038/s41433-019-0603-z

[42] Atropine disease interactions. Drugs.com Drug Interactions Checker. Available from: https://www.drugs.com/disease-interactions/atropine.html#:~:text=Anticholinergics%20(Includes%20atropine)%20%E2%86%94%20obstructive%20
In general, the use of, occur and may require catheterization. Accessed 8/15/20

[43] Jowkar A. Myasthenia Gravis. Medscape. Available from: https://emedicine.medscape.com/article/1171206-overview Accessed 6/15/20

[44] Anonymous. Learning Radiology. Colonic pseudo-obstruction. Available from: http://www.learningradiology.com/archives2011/COW%20465-Ogilvies/ogilviescorrect.htm Accessed 6/15/20

[45] Klabunde RA. Cardiovascular pharmacology concepts- Atropine (muscarnic receptor antagonist). Available from: https://www.cvpharmacology.com/antiarrhy/atropine Accessed 6/15/20

[46] Myint PK, Fox C, Kwok CS, Luben RN, Wareham NJ, Khaw KT. Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study. Age Ageing. 2015;44(2):219-225. doi:10.1093/ageing/afu185

[47] Dweik RA. Role of anticholinergic therapy in COPD. Up-to-Date. com Available from: https://wwwuptodate.com/contents/role-of-anticholinergic-therapy-in-copd?search=Anticholinergic%20therapy%20in%20COPD&source=search_result&selectedTitle=1-150&usage_type=default&display_rank=1#H91301605 Literature review current through: Jul 2020. | This topic last updated: Jun 06, 2019. Accessed 8/15/20

[48] Yuan W, Nie S, Wang H, Xu Q, Jia N. Anticholinergics aggravate the imbalance of the autonomic nervous system in stable chronic obstructive pulmonary disease. BMC Pulm Med. 2019;19(1):88. Published 2019 May 9. doi:10.1186/s12890-019-0848-0 Available from: https://bmc pulmmed.biomedcentral.com/track/pdf/10.1186/s12890-019-0848-0 Accessed 8/15/20

[49] Vetrano DL, La Carpia D, Grande G, et al. Anticholinergic medication burden and 5-Year risk of hospitalization and death in nursing home elderly residents with coronary artery disease. J Am Med Dir Assoc. 2016;17(11):1056-1059. doi:10.1016/j.jamda.2016.07.012

[50] Anonymous. Antimuscarinic therapy and cardiac safety in older patients with overactive bladder: what clinicians need to Kkow. Consultant360. 2007 February; 15 Supplement 02A. Available from: https://www. consultant360.com/articles/antimuscarinic-therapy-and-cardiac-safety-older-patients-overactive-bladder-what-clinicians Accessed 6/20/20

[51] Rochon PA. Drug prescribing for older adults. Up-to-Date. https://www.uptodate.com/contents/drug-prescribing-for-older-adults#H6. Literature review current through: Jul 2020. | This topic last updated: Jun 08, 2020. Available from: https://wwwuptodate.com/contents/drug-prescribing-for-older-adults Accessed 8/1/20

[52] Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 2015;175(3):401-407. doi:10.1001/jama internmed.2014.7663

[53] Coggins MD. Antihistamine risks. Today’s Geriatric Medicine. 2013; 6(2): 6. Available from: https://wwwtodaysgeriatricmedicine.com/archive/0313p6.shtml Accessed 8/1/20
[54] Albert SM, Roth T, Vitiello M, et al. Over-the-counter sleep aids. Today’s Geriatric Medicine. 2016. 9(2): 20. Available from: https://www.todaysgeriatricmedicine.com/archive/MA16p20.shtml Accessed 8/1/20

[55] Holden RJ, Srinivas P, Campbell NL, et al. Understanding older adults’ medication decision making and behavior: A study on over-the-counter (OTC) anticholinergic medications. Res Social Adm Pharm. 2019;15(1):53-60. doi:10.1016/j.sapharm.2018.03.002

[56] Albert RH. End-of-Life Care: common symptoms. Am Fam Physician. 2017;95(6):356-361.

[57] Kolb H, Snowden A, Stevens E. Systematic review and narrative summary: Treatments for and risk factors associated with respiratory tract secretions (death rattle) in the dying adult. J Adv Nurs. 2018;74(7):1446-1462. doi:10.1111/jan.13557

[58] Ailabouni N, Mangin D, Nishtala PS. DEFEAT-polypharmacy: deprescribing anticholinergic and sedative medicines feasibility trial in residential aged care facilities. Int J Clin Pharm. 2019;41(1):167-178. doi:10.1007/s11096-019-00784-9

[59] Gill SS, Mamdani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med. 2005;165(7):808-813. doi:10.1001/archinte.165.7.808

[60] American Academy of Nursing. Don't administer “prn” (i.e., as needed) sedative, antipsychotic or hypnotic medications to prevent and/or treat delirium without first assessing for, removing and treating the underlying causes of delirium and using nonpharmacologic delirium prevention and treatment approaches. Choosing Wisely. June 12, 2016. Available from: https://www.choosingwisely.org/clinician-lists/nursing-medications-to-prevent-or-treat-delirium/ Accessed 8/15/20

[61] American Urogynecologic Society. Avoid using anticholinergic medication to treat overactive bladder in women older than 70. Choosing Wisely. June 24, 2020. Available from: https://www.choosingwisely.org/clinician-lists/augs-avoid-using-anticholinergic-medication-to-treat-overactive-bladder-in-women-older-than-70/ Accessed 8/15/20