Chapter

Assessing Anticholinergic Effects in Older Adults

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Abstract

Anticholinergic medications are widely used in older adults and are a common source of adverse events in this population. Common drug classes include antiarrhythmics, 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

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

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_M (skeletal muscle) and N_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_M are located at the neuromuscular junction and are involved in muscle contraction. Nn 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_M receptor agonist [4].

3. Assessment of anticholinergic burden

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 management (GEM) group and in a primary care (PC) group. 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

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.

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 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

In 1991, Dr. Mark Beers published explicit criteria for the use of 'potentially inappropriate medications' or PIMS in older nursing home residents [20]. The

Drug Class	Specific Drugs
Antiarrhythmics	Disopyramide
Antidepressants	Amitriptyline, amoxapine, clomipramine, desipramine, doxepin (> 6 mg), imipramine, nortriptyline, paroxetine, protriptyline, trimipramine
Antiemetics	Prochlorperazine, promethazine
First Generation Antihistamines	Brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine (oral), doxylamine, hydroxyzine, meclizine, clidinium-chlordiazepoxide, dicyclomine, homatropine (except ophthalmic), hyoscyamine, methscopolamine, propantheline, promethazine, pyrilamine, triprolidine
Urinary Incontinence Antimuscarinics	Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium
Antiparkinsonian Agents	Benztropine, trihexyphenidyl
Antipsychotics	Chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine, trifluoperazine
Antispasmodics	Atropine (except ophthalmic), belladonna alkaloids, scopolamine (except ophthalmic)
Skeletal Muscle Relaxants	Cyclobenzaprine, orphenadrine

Table 2.
Beer's list drugs with strong anticholinergic properties.

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")

As mentioned previously, cholinergic receptors are found in various organ systems throughout the body. Blocking these receptors can have both therapeutic 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 a 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

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, acebutolol, acetylcholine

ophthalmic, aclidinium, acrivastine, alfentanil, aluminum hydroxide, amantadine, ambenonium, amitriptyline, amoxapine, arbutamine, aripiprazole, asenapine, atenolol, azatadine, belladonna, benztropine, betaxolol, bethanechol, biperiden, bisoprolol, brexanolone, brexpiprazole, brompheniramine, buprenorphine, butorphanol, calcium carbonate, carbachol ophthalmic, carbinoxamine, cariprazine, carteolol, carvedilol, cevimeline, chlorcyclizine, chlorpheniramine, chlorpromazine, cisapride, clemastine, clidinium, clomipramine, clozapine, cyclizine, cyclobenzaprine, cyproheptadine, darifenacin, demecarium bromide ophthalmic, desipramine, dexbrompheniramine, dexchlorpheniramine, dezocine, dicyclomine, dimenhydrinate, diphenhydramine, disopyramide, doxepin, doxylamine, echothiophate iodide ophthalmic, edrophonium, eluxadoline, ethanol, fesoterodine, flavoxate, flibanserin, fluphenazine, glycopyrrolate, glycopyrronium topical, guanidine, haloperidol, hydroxyzine, hyoscyamine, iloperidone, imipramine, incobotulinumtoxin A, ipratropium, isoflurophate ophathalmic, kaolin, ketoconazole, labetalol, lasmiditan, levodopa, loperamide, loxapine, lumateperone, lurasidone, macimorelin, magaldrate, magnesium carbonate, magnesium hydroxide, maprotiline, meclizine, memantine, mepenzolate, mesoridazine, methdilazine, methotrimeprazine, methscopolamine, metoclopramide, metoprolol, molindone, nadolol, nalbuphine, nebivolol, neostigmine, nortriptyline, olanzapine, olopatadine nasal, onabotulinumtoxin A, orphenadrine, oxybutynin, paliperidone, penbutolol, perphenazine, phenindamine, phenylephrine, physostigmine, pilocarpine, pimozide, pindolol, prabotulinumtoxin A, pramlintide, prochlorperazine, procyclidine, promazine, promethazine, propantheline, propiomazine, propranolol, protriptyline, prucalopride, pyridostigmine, pyrilamine, quetiapine, quinapril, remifentanil, revefenacin, rimabotulinumtoxin B, risperidone, scopolamine, sodium bicarbonate, solifenacin, sotalol, sufentanil, thiethylperazine, thioridazine, thiothixene, timolol, tiotropium, tizanidine, tolterodine, trifluoperazine, triflupromazine, trihexyphenidyl, trimeprazine, trimipramine, tripelennamine, triprolidine, trospium, umeclidinium and ziprasidone [40].

7. Contraindications to the use of anticholinergic agents

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].

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].

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].

Stimulation of M1 and M2 receptors in the GI tract increases GI motility. Anticholinergics block these receptors resulting in slowed GI motility. Ogilive'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 anticholinergic 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 cardiopulmonary 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 ≥ 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

Anticholinergic medications are readily available over-the-counter. First generation 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 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.

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