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Impact of anticholinergics on the aging brain: a review and practical application

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Objective: in an effort to enhance medication prescribing for older adults and reduce the burden of cognitive impairment, this paper reviews the literature regarding the negative impact of anticholinergics on cognitive function and provides clinicians with a practical guidance for anticholinergic use in older adults. **Methods:** a Medline search identified studies evaluating the use of anticholinergics and the relationship between anticholinergics and cognitive impairment. **Results:** prescribing anticholinergics for older adults leads to acute cognitive impairment and, possibly, chronic cognitive deficits. Assessing anticholinergic burden with a simple scale may represent a useful noninvasive tool to optimize geriatric pharmacotherapy. **Conclusion:** more studies are needed to validate the Anticholinergic Cognitive Burden scale and establish therapeutic guidelines in the presence of cognitive anticholinergic adverse effects.

Background & significance

Medications with anticholinergic activity (anticholinergics) are commonly prescribed to the 36 million older Americans for treating conditions such as allergies, depression, hypertension, Parkinson's disease, vertigo, asthma, cardiovascular disease, incontinence, psychotic symptoms and behavioral problems [1,2]. Older adults are particularly vulnerable to anticholinergic-related cognitive effects for two main reasons. First, older adults have a high probability of being exposed to anticholinergics owing to their high medical comorbidity and their use of multiple prescribed and over-the-counter medications [3-5]. Second, older adults are more sensitive to develop serious anticholinergics-related cognitive adverse effects owing to their age [6]. Aging is accompanied by a decline in hepatic and renal drug metabolism, an increase in blood-brain barrier permeability and a reduction in central cholinergic activities [6,7].

Our article provides first a review of the literature regarding the prevalence of anticholinergics and the relationship between anticholinergic exposure and cognitive impairment; and second, the article offers real-world clinicians practicing at hospital, ambulatory and long-term healthcare settings a practical guide for the use of anticholinergics, which aims to enhance the safety and quality of prescribing of these medications for older adults. This contribution to existing knowledge hopes to assist with identification of the burden of anticholinergics and, thus, reduce the risk for developing adverse cognitive outcomes such as dementia and delirium.

What is the burden of cognitive impairment among older adults?

The aging of the US population has been accompanied by a dramatic rise in the prevalence of cognitive impairment [101]. Cognitive impairment in older adults includes a variety of disorders ranging from mild cognitive impairment (MCI) and delirium to overt dementia. Dementia is an acquired syndrome of progressive decline in memory and at least one other cognitive domain, such as language, visuospatial or executive function, to an extent that is sufficient to interfere with social or occupational functioning in an alert person [8]. Delirium is an acute disturbance of consciousness with reduced ability to focus, sustain or shift attention that occurs over a short period of time and tends to fluctuate over the course of the day [9]. MCI with no dementia is defined as the presence of cognitive deficit with the absence of delirium that is not affecting the individual's functional performance [10]. Delirium and dementia are the underlying causes of cognitive impairment among the majority of hospitalized older adults [11], whereas MCI and dementia are the main causes of cognitive impairment outside hospital [12].

Depending on the method used to define cognitive impairment (delirium, MCI or dementia) and the clinical setting (hospital, nursing home or primary care), its prevalence among older adults ranges from 6 to 66% [9,11-13]. Cognitive impairment causes a high burden of suffering for patients and their families [9,101]. For patients, in addition to cognitive and functional deterioration, cognitive

impairment leads to behavioral and psychological complications, increased use of health and social services, complicated clinical management of other comorbid conditions and increased risk for medical complications such as falls, motor vehicle accidents, incontinence, fractures and infections. For family caregivers, cognitive impairment can lead to higher levels of anxiety, depression, use of psychotropic medications and chronic fatigue [12,101]. According to the Global Burden of Disease estimates for the 2003 World Health Report, dementia in particular contributed to 11% of years lived with disability in people aged 60 years and older; more than cardiovascular disease [14]. By 2050, Medicare will be spending over US\$1 trillion on beneficiaries suffering from dementia [15].

What is the role of the central cholinergic system in cognitive impairment?

The role of the central cholinergic system in cognitive impairment was discovered more than three decades ago [16–18]. Multiple human and animal studies consistently demonstrated that numerous problems in the central nervous cholinergic system lead to both cognitive and noncognitive symptoms [9,16–19]. Some of these cholinergic system abnormalities include changes and modifications in choline transport, acetylcholine release, nicotinic- and muscarinic-receptor expression, neurotrophin support and axonal transport [16–18]. The dysfunction of the cholinergic neurons throughout the basal and rostral forebrain pathways leads to a low level of the neurotransmitter acetylcholine, which contributes substantially to the cognitive impairment and behavioral symptoms of patients with Alzheimer's disease, Lewy body dementia, vascular dementia and even delirium [6,9,10,16–18].

Early work on developing animal and human models for delirium and dementia was based on the use of agents blocking the central nervous muscarinic and nicotinic receptors, such as scopolamine, atropine, pirenzepine and mecamlamine [9,17,18,20–23]. In addition, administration of scopolamine has been shown to reduce hippocampal activation on functional MRI during cognitive tasks [20]. Furthermore, lesions in animals and humans that damage cholinergic input to the neocortex or hippocampus from the basal forebrain lead to the same cognitive impairment induced by anticholinergics [6,9,10,16–18].

The above cholinergic-loss hypothesis has been the underlying justification for the current cholinergic enhancement therapy for patients with dementia, including the four US FDA-approved cholinesterase inhibitors for the treatment of Alzheimer's disease and Parkinson's disease dementia [10,17,18,101]. The use of cholinesterase inhibitors improves the cognitive symptoms of patients and might slow the progression of Alzheimer's disease. Furthermore, concomitant use of cholinesterase inhibitors and anticholinergics may result in pharmacological antagonism [7,24]. In fact, the use of anticholinergics such as atropine has been successful as an antidote for cholinesterase-inhibitor overdose [25].

More recently, a new hypothesis has been emerging that connects the effect of anticholinergics to the pathogenesis of Alzheimer's disease. This hypothesis states that long-term exposure to anticholinergics may be associated with increased Alzheimer-type pathology. Perry *et al.* found that amyloid plaque densities were more than 2.5-fold higher in Parkinson's disease patients treated with anticholinergics and that neurofibrillary tangle densities were also highest among the chronic users by comparison with the untreated or acutely-treated groups [26]. The above data suggest that blockade of cholinergic transmission might lead to the development of both acute and chronic cognitive impairment.

How can we determine the central anticholinergic effect of medications?

Although the use of anticholinergics has been part of the routine treatment of common medical conditions in the elderly, the adverse effects of these anticholinergics, as represented by atropine and scopolamine, have been known for centuries. This includes peripheral effects such as dry mouth, tachycardia, urinary retention and constipation, and CNS effects such as cognitive impairment, behavioral excitation, attention deficits and hallucinations [6]. Although therapeutic anticholinergics are well recognized by clinicians, such as oxybutinin for urinary incontinence and ipratropium for chronic obstructive pulmonary disease, other medications have anticholinergic effects as secondary, unintentional effects. Many of these medications are not well recognized by clinicians, such as antihistamines, antidepressants and neuroleptics. Furthermore, some medications have very limited anticholinergic effects but might lead to clinically significant anticholinergic effects if used in combination with other anticholinergics [6,7].

Determining the anticholinergic properties of various medications may be quantified by three methods:

- Serum radioreceptor anticholinergic activity assay (SAA) [5,28,29]
- *In vitro* measurement of drug affinity to muscarinic receptors [27]
- Expert-based list of medications with anticholinergic activity [5,30–32]

The first method of SAA quantifies a person's overall anticholinergic burden caused by all drugs and their metabolites. SAA uses tritiated quinuclidinyl benzilate as a high and specific affinity agent that competes with other anticholinergics for the muscarinic receptors [33]. SAA measures the cumulative anticholinergic effect of all prescribed or over-the-counter medications taken by the patient but reflects a transitional state outside the brain. Cognitive impairment has been reported with several drugs despite normal SAA concentrations [34] and several epidemiological studies reported no association between SAA and number of anticholinergic drugs taken by patients [5,35,36]. The second method to measure anticholinergic activity of medications uses the same radioreceptor assay as in SAA but is performed in an *in vitro* sample. It measures the binding of a specific medication into a specific muscarinic receptor, and quantifies the antagonistic properties with a comparative cholinergic agonist, leading to a measurement of the direct anticholinergic effect [27]. Translating the result of this method into the clinical world might be limited to drugs with clear peripheral anticholinergic properties with limited estimation of the drug's central or cognitive anticholinergic properties [27]. The third method is based on the opinions of clinicians, pharmacists and pharmacology researchers who combine their expertise with drug information available in the literature to determine the anticholinergic properties of certain medications. This method is the most clinically relevant method but it is the least standardized method [27]. At the current stage of research, Rudd *et al.* believe that the only method clinically useful for measuring the cognitive or central anticholinergic effects of drugs is the expert-based drug list [27].

What is the prevalence of anticholinergics use in older adults?

Older adults are prone to suffer from multiple acute and chronic conditions and, therefore, may be prescribed several anticholinergics [30]. Among the top 25 medications most commonly

prescribed for elderly patients, ten of them had recognizable anticholinergic effects [29]. Despite the development of criteria aimed at identifying drugs with anticholinergic activity as inappropriate for use by older adults [37], the utilization of such agents range from 14 to 50%, depending on the definition of anticholinergic, the prevalence method and the settings [4,5,30,31,37,38].

In the primary care urban setting, we estimated that 60% of approximately 4000 older adults received at least one anticholinergic [11,30]. In another study that randomly recruited 372 elderly people from general practices in France, 14% were taking at least one anticholinergic and 2% were taking more than two anticholinergics. At a 1-year follow-up, 59% of these study subjects were still taking anticholinergic drugs regularly and 41% had stopped taking anticholinergic drugs during the year, while 1% of the cohort had started taking them [31]. In nursing homes, more than 30% of elderly residents take more than two anticholinergics, and 5% take more than five [4,38]. In a longitudinal follow-up study of 1627 older, rural community-residing patients, diphenhydramine as a sleeping aid with a strong central anticholinergic effect was reported by 8% of participants and its use has increased from 0.4 to 8% as the cohort aged from a mean of 73.4 to 80.5 years [39]. Furthermore, in randomly selected community-dwelling elders, serum anticholinergic activity was detectable in 90% of the sample; 51% received at least one anticholinergic [5].

Is there association between cognitive impairment and the exposure to anticholinergic medications?

A review of 80 studies found a significant association between the use of anticholinergics and postoperative delirium [7]. Furthermore, Tune *et al.* also found delirium occurred in demented patients as a result of anticholinergic activities [40]. They noticed that this adverse effect does not arise from exposure to individual medications with strong anticholinergic properties, but as an accumulation of anticholinergic effects from multiple medications [32].

In a systematic evidence review of the literature, we found 13 published longitudinal cohort and case-control studies that evaluated the relationship between the use of anticholinergic and cognitive impairment, including dementia, delirium and MCI [41]. Cognitive performance was evaluated using the Mini-Mental State Examination (MMSE) in most studies. Delirium was clinically diagnosed using the Diagnostic and Statistical

Manual of Mental Disorders, 4th Edition (DSM-IV) criteria or using their derivatives, such as the Confusion Assessment Method (CAM). Anticholinergic activities were evaluated using the SAA or the expert-based drug list. All of the 13 studies found an association between the anticholinergic activity of a drug and either cognitive impairment or delirium. However, we found only one longitudinal study that evaluated the long-term exposure to anticholinergics and the risk of developing dementia or MCI [31]. In this study, among the 297 consistent nonusers of anticholinergic drugs, MCI was diagnosed in 105 (35%). Among the 30 consistent users of anticholinergic drugs, 24 (80%) met the MCI criteria [31]. Although the consistent users of anticholinergic drugs were significantly more likely to have a diagnosis of MCI at 1-year follow-up than consistent nonusers, there were no differences in overall dementia rates at 8-year follow-up between the drug users (16%) and nonusers (14%) [31]. In another longitudinal study that did not specifically evaluate the association between anticholinergics and dementia but focused on cognitive decline, Bottiggi *et al.* used retrospective data from a longitudinal elderly cohort at one of the Alzheimer's Disease Research Center [42]. The study participants received annual mental status evaluations and physical examinations. This study divided the participants into two groups: those taking one or more anticholinergics and those not taking any. Cognitive data were collected from a total of five consecutive annual visits after the baseline visit. A thorough literature search was conducted to derive a list of commonly prescribed anticholinergics. The study found that anticholinergic use did not lead to an accelerated rate of decline in global cognitive status, but it did lead to an accelerated rate of decline in scanning and visuomotor tracking and components of executive functioning, such as attention, sequencing, concentration and cognitive flexibility [42]. Finally, Roe *et al.* conducted a retrospective cohort study of 836 community-dwelling older adults to compare the prevalence of anticholinergic use in older adults with probable dementia with that of a matched comparison group of older adults who were unlikely to have dementia. They used the pharmacy claim data as the source for determining both the presence of dementia and measure exposure to anticholinergics. Patients taking donepezil (n = 418) constituted the dementia group. Patients not taking donepezil (n = 418) constituted the comparison group. The prevalence of anticholinergic use was compared in the treatment and comparison

groups over a 3- to 12-month follow-up period. This study found that older adults with probable dementia were more likely to use anticholinergics than matched comparison group patients (33 vs 23%, respectively) [2].

How can we translate the finding from the literature to the clinical setting?

Development of the Anticholinergic Cognitive Burden scale

Reviewing the literature strongly supports that the use of anticholinergics leads to acute and possibly chronic cognitive impairment among older adults. While physicians are aware of the side effects of drugs from the anticholinergic family, a countless number of new drugs are launched in the market every day with 'possible' or 'definite' anticholinergic activities that remain unrecognized by many prescribers. Furthermore, the risk of adverse effects is increased by polypharmacy, not only from prescription drugs but also from over-the-counter medications in the context of comorbid chronic diseases. Most drugs with possible anticholinergic activities are likely to be ignored among the medical community [30,32]. It was reported that even some drugs regularly prescribed for delirium, such as olanzapine, haloperidol or trazodone, had some anticholinergic activities [43,44].

As a first step in reducing the cognitive burden of anticholinergic use in older adults, our interdisciplinary team developed the Anticholinergic Cognitive Burden (ACB) scale as a practical tool that identifies the severity of anticholinergic negative effects on cognition of prescribed and over-the-counter medications, and provides the clinician with a simple score that captures the accumulative anticholinergic cognitive burden resulting from the total medications taking by older adults. We searched the Medline database from 1966 to 2007 for any study that measured the anticholinergic activities of a drug and evaluated the association between such activities and the cognitive function in older adults. We extracted from each study the method used to determine such activities and the list of medications with anticholinergic activities that were associated with negative cognitive effects, including delirium, MCI, dementia or cognitive decline. This list was presented to an expert interdisciplinary team that included geriatricians, geriatric pharmacists, geriatric psychiatrists, general physicians, geriatric nurses and aging brain researchers. Subsequently, the team categorized the above medications into three classes of mild, moderate and severe cognitive anticholinergic negative effects (Table 1).

Table 1. Anticholinergic Cognitive Burden scoring of drugs.

| Score 1 | Score 2 | Score 3 |
|--------------------------|-------------------------|--------------------|
| Alimemazine | Amantadine* | Amitriptyline*† |
| Alverine | Belladone alkaloids | Amoxapine |
| Alprazolam† | Carbamazepine† | Atropine*† |
| Atenolol | Cyclobenzaprine*† | Benztropine*† |
| Brompheniramine maleate | Cyproheptadine† | Brompheniramine† |
| Bupropion hydrochloride | Empracet | Carbinoxamine† |
| Captopril† | Loxapine† | Chlorpheniramine*† |
| Chlorthalidone† | Meperidine† | Chlorpromazine*† |
| Cimetidine hydrochloride | Methotrimeprazine† | Clemastine† |
| Ranitidine* | Molindone† | Clomipramine† |
| Clorazepate† | Oxcarbazepine† | Clozapine† |
| Codeine† | Pethidine hydrochloride | Darifenacin† |
| Colchicine | Pimozide† | Desipramine† |
| Coumadin | | Dicyclomine*† |
| Diazepam† | | Dimenhydrinate† |
| Digoxin† | | Diphenhydramine*† |
| Dipyridamole† | | Doxepin† |
| Disopyramide phosphate | | Flavoxate† |
| Fentanyl† | | Hydroxyzine*† |
| Furosemide† | | Hyoscyamine*† |
| Fluvoxamine† | | Imipramine*† |
| Haloperidol* | | Meclizine*† |
| Hydralazine† | | Nortriptyline† |
| Hydrocortisone† | | Olanzapine |
| Isosorbide† | | Orphenadrine† |
| Loperamide† | | Oxybutynin*† |
| Metoprolol | | Paroxetine |
| Morphine† | | Perphenazine* |
| Nifedipine† | | Procyclidine† |
| Prednisone† | | Promazine |
| Quinidine | | Promethazine*† |
| Risperidone* | | Propentheline† |
| Theophylline† | | Pyrilamine† |
| Trazodone* | | Quetiapine |
| Triamterene† | | Scopolamine† |
| | | Thioridazine*† |
| | | Tolterodine† |
| | | Trifluoperazine* |
| | | Trihexyphenidyl*† |
| | | Trimipramine† |

A total Anticholinergic Cognitive Burden scale score of ≥ 3 is considered clinically relevant.

*The same score given by Anticholinergic Risk Scale.

†The same score given by Anticholinergic Drug Scale.

Furthermore, the interdisciplinary team established a scoring system: drugs with possible anticholinergic effects (as demonstrated by the SAA or the *in vitro* affinity to muscarinic receptors but with no clinically relevant negative cognitive effects) were given a score of 1. Drugs with established and clinically relevant cognitive anticholinergic effects were given a score of either 2 or 3, based on the drug blood–brain barrier permeability and its association with the development of delirium. All other drugs with no anticholinergic effects can be considered as having a score of zero. The total added score of different drugs taken by the patient determines the accumulative anticholinergic cognitive burden.

Using the ACB scale, we assessed the anticholinergic burden of medication among a cohort of older adults attending primary care clinics in Indianapolis (Table 2) [13]. Similar to other studies, we found a high level of anticholinergic burden with a mean ACB score of 1.9, and more than 23% of older adults were receiving at least one medication that might lead to the development of delirium.

Over the past 2 years, two similar tools have been published to help physicians recognize the adverse effects of anticholinergics among older adults [32,45]. Carnahan and colleagues have established the anticholinergic drug scale (ADS), which determined the anticholinergic property of medications based on their effects on the serum anticholinergic activity, and accordingly categorized medications from 0 to 3, with 0 signifying no known anticholinergic activity and 3 signifying marked anticholinergic activity [32]. The ADS did not use the clinical input of expert clinicians and did not focus on the cognitive effects of anticholinergics. Thus, the ADS is most likely to be a better tool than

the ACB scale in measuring the peripheral anticholinergic effects of medications. As expected, the Carnahan team found that ADS total scores were significantly associated with SAA among long-term care residents [32].

More recently, Rudolph *et al.* developed the Anticholinergic Risk Scale (ARS) [45]. The ARS attempts to measure both the peripheral and central anticholinergic effects of medications. The ARS developers reviewed the medical literature, the National Institute of Mental Health Psychoactive Drug Screening Program and the Micromedex databases to determine the anticholinergic effects of the 500 most prescribed drugs within one veteran healthcare system in Boston, MA, USA. Similar to the ACB scale, ARS ranked medications on a scale of 0 to 3 according to the level of anticholinergic effects. Using data from 249 patients aged 65 years and older attending geriatric or primary care ambulatory clinics, the authors assessed the association between the total anticholinergic burden of medications as measured by the ARS and the overall anticholinergic adverse effects as determined by a review of the medical records. The mean ARS score ranged from 0.7 points in the primary care clinic to 1.4 points in the geriatric clinic, and higher ARS scores were associated with increased risk of both peripheral and central anticholinergic effects, with a relative risk ratio ranging from 1.3 to 1.9 [45]. By comparison with the ACB, the ARS was not based on a systematic evidence review of the literature, focused on medications used in one healthcare system that serves a predominantly male population and aimed to capture both the peripheral and central anticholinergic effects of medication. Furthermore, the ARS developers include fall, dizziness and confusion in the definition of central anticholinergic adverse effects and did

Table 2. The burden of anticholinergic use among 3013 older adults attending urban primary care clinics, as determined by the Anticholinergic Cognitive Burden scale.

| Variable | Overall |
|---|-----------|
| Mean age | 73.4 |
| Female (%) | 66.6 |
| African-American (%) | 64.5 |
| Mean total ACB score (SD) | 1.9 (2.4) |
| Percentage with at least one medication with ACB score ≤1 | 61 |
| Percentage with at least one medication with ACB score = 2 | 4 |
| Percentage with at least one medication with ACB score = 3 | 20 |
| Percentage with at least one medication with ACB score = 2 or 3 | 23 |

ACB: Anticholinergic Cognitive Burden.

not use a standardized cognitive assessment such as the confusion assessment scale or the MMSE in their definition of confusion. Thus, we believe that the ACB categorization is more accurate to measure the cognitive anticholinergic negative effects of medications than the ARS or the ADS. However, the ACB, the ADS and the ARS are easily applied to drug lists in a clinical or research setting in order to determine the overall drug-related anticholinergic burden and do not require specialized laboratory testing. Table 1 provides the reader with a list of anticholinergics with negative cognitive effects as determined by the ACB, the ADS and the ARS.

Using the ACB scale in the real clinical world

The ratings of anticholinergic potency of different drugs have the potential to decrease the burden of the two most devastating cognitive disorders facing older adults; dementia and delirium. Outlining the process of using any of the three anticholinergic burden scales within the real clinical world might be very helpful. However, any utility of these scales needs to be investigated in experimental studies using randomized clinical trial methodology.

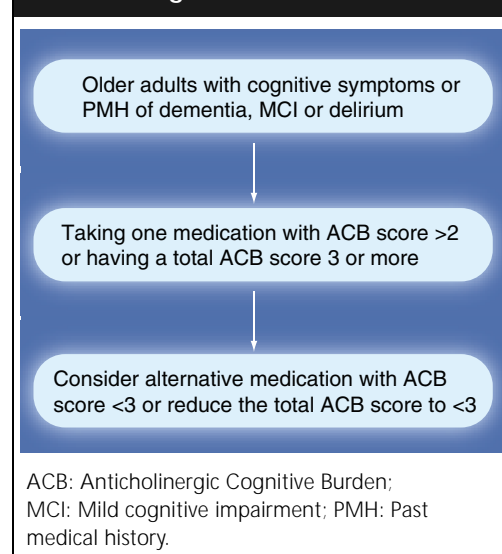
During a primary care or specialty care ambulatory visit for older people who have a past medical history of MCI, dementia or delirium, or those patients presenting with cognitive complaints, we recommend that the treating clinicians review the anticholinergic effects of all prescribed or over-the-counter medications being

taken by the patient. Using the ACB scale, a physician might consider first identifying medications with an ACB score of 2 or 3 and, second, calculate the total ACB score. In the case of an older adult prescribed a drug with an ACB score of 2 or 3, a prescriber needs to discuss with the patient the benefits and harms of continuous use of this specific drug. Together they could make an informed decision whether to switch to an alternative medication with less anticholinergic cognitive effects, hold the medication during hospitalization or acute illness, completely discontinue the drug if there is no absolute need or monitor the patient's cognitive performance regularly while receiving the anticholinergic drug. This review should include both prescribed and over-the-counter medications, particularly as some of the latter group with anticholinergic activity have been associated with cognitive impairment [11]. A similar patient–clinician informed-decision process might take place in cases where the patient is not receiving any medication with an ACB score of 2 or 3 but his/her total ACB score is above 3. Furthermore, when the withdrawal of suspected agents is appropriate, we suggest the withdrawal to occur with an appropriate, gradual schedule to avoid rebound anticholinergic or psychiatric adverse effects (Figure 1).

The case of Marie Doe

Mrs Doe is an 80 year old African–American female with past medical history of chronic heart failure (CHF), osteoarthritis, hypertension, gastroesophagus reflex disorder and mixed urine incontinence who presented to her geriatrician at the Healthy Aging Brain Center in Indianapolis, IN, USA, with a chief complaint of memory loss for the past 4 months observed by her husband. This problem started during her recent hospitalization for CHF exacerbation. In the hospital, the patient suffered from insomnia and displayed 48 h of agitated behavior such as pulling her Foley catheter. Her CHF was treated with diuretic and antihypertensive medications and her insomnia and agitation were treated with a combination of olanzepine and diphenhydramine. After the hospitalization, the patient's confusion continued to a lesser degree. Currently, the patient has short-term memory loss and psychomotor retardation but she has no language problems, attention problems or fluctuation. Her mood is stable and her insomnia is resolved. She is still independent with her basic activities of daily living,

Figure 1. Practical guide to assess anticholinergic burden in older adults.



but requires some assistance in taking her medications. Her current drug list includes olanzepine, furesomide, cardizam, omeprazole, acetoaminophen, digoxin, oxybutynin, multi-vitamin, and calcium with vitamin D. Her physical examination revealed symmetrical neurological examination, normal gait and no evidence of acute infection process. Her MMSE score was 20, her confusion assessment method was negative for delirium. Her geriatrician calculated her total ACB score to be 8 points and identified oxybutynin and olanzepine as drugs with an ACB score of 3. He discussed the negative anticholinergic effects of the above two medications with Mrs Doe and her husband, who selected to stop olanzepine and oxybutynin. The geriatricians suggested alternative nonpharmacological intervention for her urine incontinence and a follow-up visit. By 3 months later, Mrs Doe's MMSE score increased to 23 and her ACB score was 2.

Conclusion & future perspective

As the number of older adults suffering from both cognitive impairment and multiple chronic conditions that require management with numerous medication increases, it is important to recognize the negative impact of medication

on the aging brain. It is conceivable and valuable to create a process within the new drug approval system of the US FDA that provides data on the anticholinergic cognitive effects of every medication targeting older adults. These important data can then be translated into feasible and useful decision-support tools that enhance geriatric pharmacotherapy. More studies are needed, however, to validate all of the three ACB scales as well as establish therapeutic guidelines in the presence of suspected or established cognitive anticholinergic adverse effects.

In a world of increasing pharmacological complexity, the integration of the ACB scale into decision-support systems may have the potential to improve patients' outcomes by improving cognitive functioning.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

| Executive summary |
|---|
| <p>Background & significance</p> <ul style="list-style-type: none"> • Medications with anticholinergic activity are commonly prescribed to older adults. • Older adults are vulnerable to anticholinergic-related cognitive effects. |
| <p>What is the burden of cognitive impairment among older adults?</p> <ul style="list-style-type: none"> • Depending on the method used to define cognitive impairment and the clinical setting, approximately 6–66% of older adults suffer from cognitive deficits. • Cognitive impairment causes a high burden of suffering for patients and their families. |
| <p>What is the role of the central cholinergic system in cognitive impairment?</p> <ul style="list-style-type: none"> • Blockade of cholinergic transmission might lead to the development of both acute and chronic cognitive impairment. |
| <p>How can we determine the central anticholinergic effect of medications?</p> <ul style="list-style-type: none"> • The most clinically useful method to determine the anticholinergic cognitive effects of drugs is the expert-based drug list. |
| <p>What is the prevalence of anticholinergics use in older adults?</p> <ul style="list-style-type: none"> • In the primary care urban setting, approximately 60% of older adults receive at least one anticholinergic. |
| <p>Is there an association between cognitive impairment & exposure to anticholinergic medications?</p> <ul style="list-style-type: none"> • Anticholinergics for older adults lead to acute cognitive impairment and possibly chronic cognitive deficits. |
| <p>How can we translate the finding from the literature to the clinical setting?</p> <ul style="list-style-type: none"> • Assessing anticholinergic burden with the Anticholinergic Cognitive Burden scale may represent a useful noninvasive tool to optimize geriatric pharmacotherapy. |
| <p>Future perspective</p> <ul style="list-style-type: none"> • We need to build a process within the new drug approval system of the US FDA that provides data on the anticholinergic cognitive effects of every medication used by older adults. |

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