Assessing the health implications of anticholinergic drugs in older people

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Abstract

In this narrative review, we analyzed the existing literature on the pros and cons of anticholinergic medications, focusing on their prevalence, underlying mechanisms, and methods of assessment. Our review underscores the significant adverse effects of anticholinergic drugs, particularly on cognition and functional abilities in older adults. These effects include the exacerbation of various cognitive states, increased psychiatric symptoms, heightened risk of delirium, functional decline, elevated hospitalization rates, greater likelihood of institutionalization, and increased mortality. While anticholinergic medications provide therapeutic benefits, their use in older adults requires careful evaluation due to these considerable risks. Discontinuation of anticholinergic therapy offers both benefits and challenges. We propose practical guidelines for their use in clinical contexts such as dementia, schizophrenia, depression, anxiety, Parkinson's disease, cardiovascular conditions, and urinary incontinence.

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Key words: aging, cognition, drugs, geriatrics, older, psychiatry.

Contributions: MB, drafting the work and analysis of literature; VB, conception, analysis, revising.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Patient consent for publication: not applicable.

Funding: none.

Availability of data and materials: all data underlying the findings are fully available.

Received: 28 October 2024.
Accepted: 5 December 2024.

Licensee PAGEPress, Italy
Geriatric Care 2025; 11:13311
doi:10.4081/gc.2025.13311

Introduction

As our population continues to age, concerns regarding the cognitive and functional well-being of older individuals become increasingly important. Among the various factors influencing cognitive decline and functional impairment in this demographic, the use of anticholinergic drugs has emerged as a subject of significant interest and concern.[1] Anticholinergic drugs, commonly prescribed for a range of conditions, including allergies, gastrointestinal disorders, and neurological conditions, exert their effects by blocking the neurotransmitter acetylcholine in the central and peripheral nervous systems (CNS and PNS, respectively).[2] While these drugs serve important therapeutic uses, mounting evidence suggests that their prolonged use may be associated with adverse effects on cognitive function and daily functioning. This narrative review aims to provide a comprehensive understanding of the risks posed by this kind of drug in older people. By synthesizing existing research findings, elucidating underlying mechanisms, and discussing clinical implications, this review aims to better clarify the risks associated with the use of these medications in older people.

Methods

We conducted a literature search in the PubMed, Medline, and Cochrane databases on April 1, 2024, to identify all articles published with the medical subject heading keywords "aging", "anticholinergic", "drug", "health", "cognition", "outcomes", "functional", and "older". The key words were utilized in various combinations to maximize the retrieval of relevant articles, encompassing studies ranging from bench and animal models to clinical trials. While priority was given to the most pertinent research, publications highlighting areas of interest were also included.

The consequences of aging

The aging process is defined as a complex set of structural and functional changes affecting various organs, systems, and body, resulting in a progressive loss of adaptability to the environment. Individuals become increasingly susceptible to developing diseases,

ultimately leading to death.[3] The aging of the population is a phenomenon that has characterized Western countries for more than half a century, posing significant challenges to societies and presenting a cultural, social, economic, and political challenge to which institutions have not yet found an adequate solution.[4] In 1950, the population graph resembled a pyramid, with a broad base of young individuals tapering upwards. Today, in the "completed demographic transition" phase, it has taken on a spindle shape, dominated by middle-aged groups. In the coming decades, it will likely resemble an inverted pyramid, with older populations outnumbering younger ones. This "demographic revolution" stems from increased life expectancy, declining birth rates, and the "baby boom" phenomenon.[4,5] The increase in life expectancy is due to two main factors: the reduction in child mortality from infectious diseases in the early 20th century, thanks to improved hygiene, sanitation, antibiotics, and vaccinations, and a more recent decline in mortality among older adults due to advances in prevention and treatment, particularly for cardiovascular diseases. This demographic transition reflects a shift from infectious diseases to chronic degenerative conditions in aging societies.[6] The presence of such diseases, in addition to increasing mortality, leads to an increased risk of developing disabilities, defined as the inability or difficulty in performing activities of daily living necessary for autonomy both at home and outside. The rapid aging of the population has significant consequences, particularly in healthcare, leading to rising costs from increased hospitalizations and long-term care needs. Experts are divided on future outcomes: some predict that advances in lifestyle and medical science will reduce late-life morbidity and disability, while others foresee an expansion of age-related diseases, resulting in longer lives but poorer health and autonomy.[7]

The unique characteristics of older patients: comorbidity and polypharmacy

The definition of aging is open to various interpretations, although it is commonly agreed upon that aging is the sum of all physiological, biological, and molecular changes that occur over time, from birth to death. The older adult represents a highly heterogeneous group of the population; there are healthy individuals, and there are subjects of advanced or very advanced age, chronically affected by multiple diseases, with unstable health status, and frequently disabled, known as frail.[8] In the "frail" phenotype, several domains have been identified, such as critical socio-environmental status, reduced functional autonomy, advanced aging, the coexistence of chronic diseases, and polypharmacy, which interact with each other, determining and characterizing frailty.[9] Frail older adults have unique needs affecting clinical and organizational care. They face a higher risk of chronic, progressive, and disabling diseases than younger individuals. Advances in managing chronic illnesses have extended life expectancy, leading to a significant rise in multimorbidity, the coexistence of multiple chronic conditions.[10]

Quantifying and describing multimorbidity in older adults is crucial due to its impact on healthcare demand and its strong link to disability. Many individuals with diagnosed conditions also have undetected illnesses due to atypical presentations, silence of symptoms, or preclinical stages. Thus, defining multimorbidity solely by counting evident diseases is considered reductive, as it fails to capture the full extent of health compromise.[9] Much has been discussed in recent years about multimorbidity and comorbidity, although it is necessary to distinguish between two terms that are now recurring in the literature but are too often still overlapped in clinical practice. Multimorbidity is defined as a situation in which multiple chronic diseases coexist in the same individual. This shifts the focus to the potential consequences of pathologies in the individual without referring to a disease considered primary, as it is the patient who is put in the forefront.[11] Comorbidity, on the other hand, refers to patients affected by a chronic disease considered as primary; thus, the role that other chronic pathologies play in influencing its clinical expression, evolution, and prognosis.

A prominent repercussion of multimorbidity is the phenomenon known as polypharmacy, typically characterized by the routine consumption of five or more distinct medications daily. This practice is particularly prevalent among older individuals.[12] Within the scope of this definition, the prescription of medications lacking evidence-based justification, or those that have become ineffective or potentially hazardous due to adverse drug reactions (ADRs), ought to be recognized as instances of inappropriate polypharmacy. The term "adverse drug reaction" refers to "any harmful, unintended reaction to a drug occurring at doses normally used in humans for prophylaxis, diagnosis, or therapy".[13] Currently, the more accurate term considered is adverse drug events (ADEs).[14] In the older, ADEs/ADRs, instead of recognizing a single causal factor, as usually occurs in young adults, are attributable to a multiplicity of interacting factors; moreover, the older, given their characteristics, are certainly at higher risk. In general, ADEs can be attributed to various causes: i) errors in prescription and/or monitoring (inappropriate prescription); ii) errors in administration (by caregivers, nurses, or family members); iii) errors in intake (non-adherence).

Polypharmacy poses challenges in bridging theoretical knowledge with practical application, especially for older patients on multiple medications. Factors like pharmacokinetic and pharmacodynamic changes, comorbidities, drug interactions, frailty, and fragmented care increase their risk of adverse events and severe iatrogenic diseases. Many high-risk medications are commonly used to treat chronic age-related conditions, and older patients often require long-term polytherapy for multiple chronic illnesses.[14,15]

Therapeutic inappropriateness in the older person

The concept of inappropriate prescription, where drug risks outweigh benefits or deviate from medical standards, is increasingly relevant. Examples include prescribing antihypertensives like clonidine, methyldopa, and doxazosin in monotherapy or short-acting calcium antagonists. A study on older adults with dementia found most had received inappropriate prescriptions in the past year, increasing their risk of hospitalization and institutionalization.[16] Given the significant implications that inappropriate drug prescription has on the patient and the National Health Service, various methods have been proposed to avoid falling into this error. One proposal has been to identify classes of drugs or specific drugs that, when administered to the older, are always inappropriate or they are when prescribed in the presence of certain pathologies. While specializing in pharmacovigilance in nursing homes, Mark Beers, an American geriatrician who died in 2009, noticed that many of the psychotropic drugs frequently used induced more adverse effects than benefits. In 1988, he published his data, highlighting the enormous gaps in clinical documentation regarding the therapy of older patients, thus putting them at risk of serious prescribing errors.[17] The first version of Beers' pharmacological criteria was published in 1991 in the Archives of Internal Medicine, focusing on the possible adverse effects of sedatives, muscle relaxants, antihistamines, and antidepressants. After a further study in 2003, also published in the Archives of Internal Medicine, an update of these criteria was published, including many other molecules, indicating over 40 drugs or categories of drugs as potentially risky, inappropriate, or ineffective.[18] These criteria still constitute the basic reference for pharmacological prescription surveillance in favor of the older.[19]

Different is instead the methodology proposed by Hanlon *et al*., which involves the use of the so-called index of appropriateness of drug prescription, constructed considering ten different aspects of medical prescription: indication, effectiveness, dosage, patient education by the physician, feasibility, interactions with other drugs, interactions with other pathologies, unnecessary duplication, treatment duration, and cost.[20] Using this index, it was possible to demonstrate that 74% of 1644 drugs prescribed on an outpatient basis to 208 older patients had been subject to inappropriate prescription, particularly concerning patient education, dosage, and costs.[21]

To better rationalize drug prescription in the older, the "STOPP" (Screening Tool of Older Persons Prescriptions) and "START" (Screening Tool Alert Doctors to Right Treatment) criteria have been proposed.[22,23] These criteria, compared to those of Beers, have the following advantages: they are rapid and easy to use, they include under-prescription and medication duplication, they are organized by systems, and they consider the most used drugs in Europe. More specifically: i) STOPP criteria identify potentially inappropriate drugs that should be discontinued or replaced with safer alternatives, as well as the possible therapeutic implications and impact on cognitive abilities and the risk of falling; ii) START criteria, on the other hand, consider drugs that are generally under-prescribed by doctors due to fear of adverse events, even in the absence of clear contraindications.

Adverse anticholinergic effects of drugs

Despite extensive efforts in research and clinical practice, inappropriate medication use remains prevalent among older patients. One of the most discussed categories of inappropriate prescriptions in older people involves medications with anticholinergic adverse effects. These drugs, known for their potential to cause cognitive impairment, falls, and other adverse outcomes, continue to pose significant challenges in optimizing medication regimens for older adults.[2]

These types of adverse effects can be divided into two categories, peripheral and central and reported in Table 1. As peripheral, it has been reported reduced salivation, bronchial and sweat secretions, inhibition of accommodation, mydriasis, urinary retention, tachycardia, and reduced gastrointestinal motility. These symptoms, which should be straightforward to diagnose for any physician, are often underestimated despite their potential to lead to very serious complications, ranging from ulcerative gingivitis to respiratory problems to hyperthermia and myocardial infarction.

Anticholinergic medications act by binding to muscarinic receptors, disrupting acetylcholine neurotransmission crucial for various bodily functions. These functions span both CNS, encompassing attention, learning, and memory, and PNS, governing basic physiological activities such as urination, intestinal transit, and heart rhythm regulation. Anticholinergic drugs may target muscarinic receptors exclusively or also interact with other receptors, leading to diverse therapeutic effects and nomenclature variations (*e.g*., tricyclic antidepressants). Given the broad involvement of cholinergic transmission in physiological processes, anticholinergic drugs can elicit adverse effects impacting both the CNS and PNS. Adverse effects on the CNS may manifest as cognitive dysfunction across various domains, cognitive decline, hastened neurodegenerative processes, emergence of psychotic or delirious symptoms, and disruptions in functionality. Conversely, adverse effects on the PNS include dry mouth, urinary retention, constipation, paralytic ileus, increased heart rate, and blurred vision, among others.[1]

Anticholinergic medications find application across various medical conditions including urinary dysfunction, peptic ulcer disease, irritable bowel syndrome, and Parkinson's disease. Additionally, they are commonly employed as anesthetic agents and for addressing neurologic and psychiatric disorders.[24,25] While certain anticholinergic drugs are widely recognized for their effects, there are others with lesser-known anticholinergic activity (AA). The primary characteristics of anticholinergic drugs stem from their interactions with central and/or peripheral cholinergic receptors.[2] These interactions can induce symptoms such as cognitive impairments, which may mistakenly be attributed to normal aging processes. It is worth noting that certain medications, including amoxicillin, diazepam, digoxin, duloxetine, fentanyl, furosemide, lansoprazole, metformin, phenytoin, or topiramate, exhibit AA only at high doses. Additionally, the concurrent use of different medications (or even dietary supplements like chondroitin or certain vitamins) can precipitate or intensify the adverse effects associated with a prescribed anticholinergic drug.[25]

Of relevance is the association between cognitive impairment and the use of drugs with anticholinergic properties, which is well known in the literature, although it has been underestimated for many years, leading to the continued prescription of these drugs in many older patients. These types of drugs are commonly used for the treatment of common diseases such as asthma, urinary incontinence, and various psychiatric disorders.[26] Additionally, many over-the-counter medications have potential anticholinergic effects (*e.g*., old antihistamines contained in some commonly used products, such as those for symptomatic influenza syndrome, hypnotics, antidiarrheals, and antispasmodics), and the number of such medications is increasing to the point where it is difficult to properly monitor their use. Studying the effects of these drugs is very important because it has been observed that the CNS of older patients is more sensitive to the adverse anticholinergic effects of drugs due to the significant decrease in the number of cholinergic receptors in these subjects. Reduced hepatic metabolism, reduced renal excretion of drugs, and increased permeability of the blood-brain barrier are also contributing to the phenomenon. Various effects have been linked to the administration of anticholinergic drugs, extending beyond cognitive impairment. Nonetheless, it is crucial to acknowledge the presence of reverse-causation bias when investigating this phenomenon, wherein the underlying medical condition itself, rather than the anticholinergic medication used for its treatment, may contribute to observed outcomes.[25,26] This inherent limitation is typically addressed through longitudinal studies. However, such studies are relatively scarce due to their inherent complexity and costliness. Moreover, another challenge lies in the fact that drugs exhibiting AA may interact with various receptors beyond the muscarinic receptor, potentially altering or mitigating specific side effects associated with the anticholinergic effect.[26]

Table 1. Summary of peripheral and central adverse effects of anticholinergic drugs.

Category	Adverse effects
Peripheral	Reduced salivation Inhibition of bronchial and sweat secretions Inhibition of accommodation and mydriasis Urinary retention Tachycardia Reduced gastrointestinal motility
Central	Reduced concentration Confusion Attention deficits Impairment of memory

Anticholinergic drugs: cognition and functional decline

The adverse cognitive effects of anticholinergic drugs have been scrutinized through both cross-sectional and longitudinal studies involving healthy individuals, those with mild cognitive impairment (MCI), and those with dementia. However, a consensus regarding the cognitive impact of anticholinergic drugs, as well as their reversibility, remains elusive.[27] Studies that failed to establish an association have faced scrutiny due to potential protopathic bias or reverse causation, stemming from increased usage of these drugs to manage prodromal dementia symptoms. Another confounding factor could be the utilization of the Mini-Mental State Examination (MMSE), a widely employed cognitive screening tool now under scrutiny for its ability to detect subtle drug-induced changes.[28,29]

Consequently, more comprehensive neuropsychological assessments are now being recommended. Regarding the diverse outcomes reported, another hypothesis posits that this heterogeneity may be attributed to variations in the cholinergic reserves of study participants, potentially explaining the absence of a discernible link between cognition and anticholinergic burden in middle-aged individuals. Since 1973, studies have suggested that blocking muscarinic receptors alters learning processes. Subsequent research, primarily cross-sectional, has linked anticholinergic drug use to various cognitive parameters such as episodic memory, executive functions, and psychomotor speed (reviewed in López-Álvarez *et al.*).[2] However, the evidence regarding the cognitive effects of anticholinergic drugs and whether they are reversible remains inconclusive. Cross-sectional studies have been questioned due to potential protopathic bias or reverse causation, which could skew results. Longitudinal studies are recommended to better assess cognitive dysfunction and potential links to dementia. Some studies suggest that prolonged exposure to anticholinergic drugs may accelerate cognitive decline, particularly in executive function components.[30] The intake of anticholinergics has been associated with declines in MMSE scores, regardless of functional decline.[31] While brief exposure to these drugs may lead to cognitive impairment, it is not necessarily associated with dementia.[32] However, prolonged exposure has been linked to dementia development, suggesting a potential cumulative dose effect.[33] Studies also explore the transition from cognitive normality to MCI and dementia. Continued use of potent anticholinergics may increase conversion rates to MCI.[34] The presence of the APOE 4 allele, a known risk factor for dementia, shows conflicting results regarding its influence on cognitive dysfunction mediated by anticholinergic drugs.[35,36] In summary, while anticholinergic drugs may have a self-limited impact on cognition in cognitively normal individuals, the long-term effects are still under investigation.

There is evidence that drugs with anticholinergic effects alter not only the cognitive but also the functional status of the older. Various studies have explored the relationship between anticholinergic drugs and physical and functional decline. These drugs can induce alterations both centrally and peripherally, affecting functions like visual accommodation, heart rate, and gait. While most cross-sectional and longitudinal studies associate anticholinergic load with loss of functionality, some findings contradict this.[37-39] Anticholinergic drugs impact basic activities such as bathing, grooming, and mobility, and a dose-response relationship has been observed.[40,41] They also affect functional rehabilitation following conditions like stroke or minor injuries.[40] Falls are a significant concern among the elderly, and while anticholinergic use has been associated with recurrent falls, evidence remains inconclusive.[42] The association may be influenced by dosage, treatment duration, and non-anticholinergic effects like sedation. Overall, while many studies indicate a link between anticholinergic load and functional decline, there is variability in findings.

Discussion and Conclusions

Prescribing anticholinergic drugs to geriatric patients remains inevitable in many clinical settings. Table 2 reports the principal

Table 2. Principal scales and indexes of anticholinergic drugs.

Scale	Description	Notable features
Anticholinergic Drug Scale	Classifies drugs based on their anticholinergic activity. Scores range from 0 (no activity) to 2-3 (high activity). Developed considering SAA, pharmacological characteristics, and clinical experience. Includes various medications, including non-oral formulations.	- Considers SAA - Incorporates pharmacological characteristics and clinical experience - Comprehensive coverage, including non-oral formulations
Anticholinergic Risk Scale	Rates drugs based on their anticholinergic risk level, using a scoring system from 0 to 3 points. Developed using dissociation constants of the muscarinic receptor, rates of anticholinergic effects, and a literature review of approximately 500 drugs. Mainly includes psychotropics and excludes non-oral formulations.	- Based on dissociation constants of the muscarinic receptor - Derived from a literature review of around 500 drugs - Primarily focuses on psychotropics - Excludes non-oral formulations
Anticholinergic Cognitive Burden Scale	Classifies drugs based on their cognitive effects related to anticholinergic activity. Assigns scores of 1 (mild cognitive effects), 2 (moderate cognitive effects), or 3 (significant cognitive effects). Considers SAA or *in vitro* affinity to muscarinic receptors. Commonly used in research studies.	- Considers cognitive effects related to anticholinergic activity - Incorporates SAA or *in vitro* affinity to muscarinic receptors - Widely used in research studies
Drug Burden Index	Represents the cumulative anticholinergic or sedative burden of multiple drugs. Calculated by the ratio of the prescribed dose to the sum of the minimum and prescribed doses. Values range from 0 to ∞. Includes oral, topical, and inhaled formulations. Recognized as a valuable tool for longitudinal assessment of anticholinergic effects.	- Considers cumulative anticholinergic or sedative burden - Calculated based on prescribed dose compared to minimum and prescribed doses - Covers oral, topical, and inhaled formulations - Useful for longitudinal assess

SAA, subjective anticholinergic activity.

Table 3. Principal clinical conditions and practical recommendations.

Clinical condition	Practical recommendations
Dementia	- Discontinue or reduce anticholinergic drugs, especially in dementias with cholinergic deficits such as Alzheimer's, Lewy body, and Parkinson's dementia. - Prioritize antipsychotics with minimal anticholinergic effects. - Short-term use of antipsychotics after non-pharmacological interventions.
Schizophrenia	- Minimize antipsychotic doses to avoid additional anticholinergic use for extrapyramidal side effects. - Monitor cognitive effects closely, especially in patients with baseline cognitive impairment. - Consider individual cases for anticholinergic use in acute dystonia.
Acute hallucinatory episode	- Assess and withdraw antidepressants or serotonergic drugs before prescribing antipsychotics.
Depression	- Strive for remission to prevent dementia progression. - Evaluate risks before switching from tricyclic antidepressants to SSRIs.
Anxiety	- Prefer lorazepam over other benzodiazepines due to its shorter action and lower cognitive effects.
Parkinson's disease	- Discontinue anticholinergic drugs if cognitive dysfunction occurs and avoid reintroduction.
Urinary incontinence/bladder dysfunction	- Explore non-pharmacological options first, such as lifestyle changes and physiotherapy. - Consider individual risk-benefit for anticholinergic medications; select drugs with lower anticholinergic load. - Explore alternative treatments like botulinum toxin in certain cases.

SSRIs, selective serotonin reuptake inhibitors.

scales and indexes of anticholinergic drugs that can be used in clinical practice. Thus, when necessary, preference should be given to medications with a mild anticholinergic burden and high receptor affinity. This approach can help mitigate potential cognitive and adherence issues associated with increased anticholinergic load, particularly notable in male patients. Before initiating anticholinergic therapy, it is crucial to evaluate cognitive function and consider comorbidities sensitive to anticholinergic effects, such as benign prostatic hypertrophy and gait disturbances. This assessment should include existing anticholinergic burdens from concurrent medications. Due to the risk of irreversible cognitive effects with prolonged use, continuous re-evaluation of the efficacy and risks of anticholinergic drugs is essential, particularly for treatments exceeding three months. Abrupt discontinuation is discouraged due to the potential for cholinergic rebound, characterized by symptoms such as agitation, diarrhea, and insomnia. Patients should be informed of these risks and actively participate in treatment decisions. To mitigate anticholinergic-induced iatrogenesis, leveraging clinical pharmacologists' expertise, utilizing anticholinergic load calculators, and employing tools like the Pocket Reference Card for Medicines with Anticholinergic Activity can be beneficial. Future developments in software that offer therapeutic alternatives tailored to specific clinical contexts may further optimize patient care and minimize anticholinergic-related harm. Table 3 provides concise practical recommendations for each clinical condition, emphasizing strategies to minimize anticholinergic drug use while addressing specific treatment needs.

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