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Association between anticholinergic burden and anticholinergic adverse outcomes in the elderly: Pharmacological basis of their predictive value for adverse outcomes

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ABSTRACT

The use of anticholinergic drugs and other drugs with anticholinergic activity is highly prevalent in older people. Cumulative anticholinergic effects, known as anticholinergic burden, are associated with important peripheral and central adverse effects and outcomes. Several methods have been developed to quantify anticholinergic burden and to estimate the risk of adverse anticholinergic effects. Serum anticholinergic activity (SAA) and anticholinergic burden scoring systems are the most commonly used methods to predict the occurrence of important negative outcomes. These tools could guide clinicians in making more rational prescriptions to enhance patient safety, especially in older people. However, the literature has reported conflicting results about the predictive ability of these tools. The majority of these instruments ignore relevant pharmacologic aspects such as the doses used, differential muscarinic receptor subtype affinities, and blood-brain barrier permeability. To increase the clinical relevance of these tools, mechanistic and clinical pharmacology should collaborate. This narrative review describes the rational and pharmacological basis of anticholinergic burden tools and provides insight about their predictive value for adverse outcomes.

1. Introduction

Anticholinergic drugs are often prescribed to older people for the management of different clinical conditions. However, for some drugs, their anticholinergic activity is not connected with their primary therapeutic purpose and mechanism of action (*e.g.*, antidepressants, antipsychotics and antihistamines). Approximately 20−50% of older people are routinely exposed to drugs with potential anticholinergic activity,

Abbreviations: AAS, Anticholinergic Activity Scale; ABC, Anticholinergic Burden Classification; ABS, Anticholinergic Burden Score; ACB, Anticholinergic Cognitive Burden Scale; ACh, Acetylcholine; ACL, Anticholinergic Loading Scale; AD, Alzheimer's disease; ADS, Anticholinergic Drug Scale; AEC, Anticholinergic effect on cognition; ARS, Anticholinergic Risk Scale; BBB, Blood Brain Barrier; CNS, Central Nervous System; CrAS, Clinician-rated Anticholinergic Score; DBI, Drug Burden Index; DBI-WHO, Drug Burden Index – World Health Organization; DDD, Defined Daily Dose; (G)MainD, The (Geriatric) Maintenance Dose; (G)MaxEV, The (Geriatric) Maximal Effective Dose; (G)MinEV, The (Geriatric) Minimal Effective Dose; 3H-QNB, tritiated radioligand quinuclidinyl benzilate; IADL, Instrumental activities of daily living; KABS, Korean Anticholinergic Burden Scale; MARANTE, Muscarinic Acetylcholinergic Receptor ANTagonist Exposure; MMSE, Mini-Mental State Examination; SAA, Serum Anticholinergic Activity; SmPC, Summary of Products Characteristics; SPPB, Short Physical Performance Battery.

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and 30−50% medicines commonly prescribed to older people have potential anticholinergic activity [1–4]. Institutionalization is considered an important risk factor for the prescription of anticholinergic drugs [5]. Nursing home residents use significantly more anticholinergic drugs than home-dwelling older people [6,7]. More than 30 % of nursing home residents use more than two drugs with anticholinergic activity, and 5% take more than five [8,9]. During hospital admission, the number of patients who receive drugs with anticholinergic activity increases [10], with more than 79 % of inpatients using one or more drugs with anticholinergic activity [11]. In palliative care, the anticholinergic burden increases as death approaches [12].

The wide distribution of muscarinic receptors across many physiological systems contributes to a variety of peripheral (*e.g.*, dry mouth, dry eyes, urinary retention, constipation or tachycardia) and central (*e.g.*, cognitive impairment, delirium, confusion or falls) adverse effects. Recent evidence suggests that the use of drugs with anticholinergic effects is also associated with negative endpoint outcomes, such as impaired functionality and higher hospitalization and mortality rates [13–15]. Anticholinergic adverse effects are often considered unavoidable or wrongly associated with age-related conditions [5]. Consequently, these adverse effects are frequently treated with additional medication, causing prescribing cascades [10]. Additionally, anticholinergic adverse effects of drugs concomitantly used cumulate in what is known as anticholinergic burden.

Given the potential consequences of adverse effects of drugs with anticholinergic activity in a susceptible population, several instruments were created to help clinicians to reduce the effects of anticholinergic burden. The predictive power of these instruments is under scrutiny. Thus, this narrative review aims to describe the rational and pharmacological basis of anticholinergic burden tools and provide insight about their predictive value for adverse outcomes.

2. Anticholinergic drugs

Acetylcholine (ACh) can bind to two different types of receptors. The nicotine actions of cholinergic agonists are related to the stimulation of the excitatory receptors at the autonomic ganglion cells, the adrenal medulla, and the neuromuscular junction. Muscarinic receptors are widely distributed across the body, both in central and parasympathetic nervous system, but also in sweat glands innervated by sympathetic system [16] and at enteric ganglia and vascular endothelium [17]. There are five subtypes of metabotropic muscarinic receptors (M1-M5). Subtypes M1, M3 and M5 activate phospholipase C pathway, resulting in mobilization of intracellular Ca2+, with a subsequent stimulatory response. Conversely, M2 and M4 muscarinic receptor subtypes negatively modulate adenylyl cyclase activity, reducing cAMP production, originating an inhibitory response (Fig. 1).

Drugs with predominantly antinicotinic effects are typically prescribed in surgery or intensive care for neuromuscular blockade or are limited to research environments (*e.g.*, ganglionic blockers) [16]. Anticholinergic drugs mediate their effects mostly through muscarinic receptor antagonism. Thus, the most appropriate term for this drug class should be “muscarinic receptor antagonists”, but the literature mostly presents the term “anticholinergic drugs” [18] or drugs with anticholinergic activity. Most anticholinergic drugs are nonselective for receptor binding, and the efficacy of some of these drugs comes from a balance of antagonistic actions on two or more receptor subtypes [19]. The blockade of nicotinic receptor sites attributed to these drugs is negligible [17].

Parasympathetic neuroeffector junctions in different organs have different sensitivities to anticholinergic drugs. While small doses of atropine depress salivary and bronchial secretions and sweating, larger doses cause pupil dilation, inhibition of ocular accommodation and increased heart rate. Still larger doses inhibit micturition and decrease the tone and motility of the gut, and even larger doses inhibit gastric motility and gastric secretions [17]. These different dose-response effects in various systems together with nonselective binding to muscarinic receptor subtypes make the prediction of anticholinergic adverse effects even more complicated [19,20].

More than 600 drugs have been reported as having anticholinergic activity [21]. The most commonly prescribed drugs because of their anticholinergic properties belong to a wide range of therapeutic classes that act on several physiological systems, including the cardiovascular system, respiratory system, central nervous system (CNS), gastrointestinal system, and genitourinary system. Depending on the drug, anticholinergic activity varies from low to high [4,22]. Additionally, the anticholinergic potency, a measure of anticholinergic activity, also varies depending on the affinity of the drugs for muscarinic receptors and on the numbers of available receptors to bind [1].

3. Anticholinergic adverse effects

Anticholinergic adverse effects can be categorized into peripheral and central adverse effects [5]. Peripheral anticholinergic adverse effects are determined by the blockade of muscarinic receptors that mediate muscle contraction and glandular secretions (see Fig. 2) [1,17]. Central anticholinergic adverse effects are determined by the drugs' distribution into the brain and their competitive binding affinities to cerebral muscarinic receptors (see Fig. 3) [20].

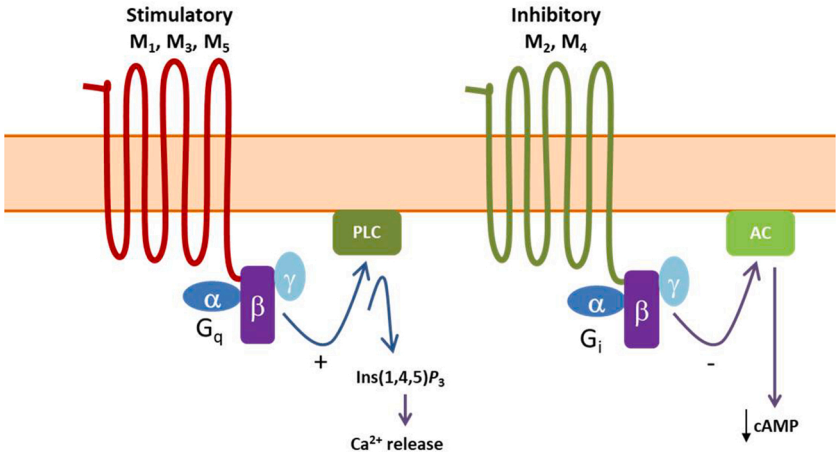

Fig. 1. Muscarinic receptor subtypes (M1-M5), their functions and post-receptor mechanisms.
AC: Adenylyl cyclase; AGq: cAMP: Cyclic adenosine monophosphate; Gq protein alpha subunit; Gi: Gi protein alpha subunit; Ins(1,4,5)P3: Inositol trisphosphate; PLC: Phospholipase C

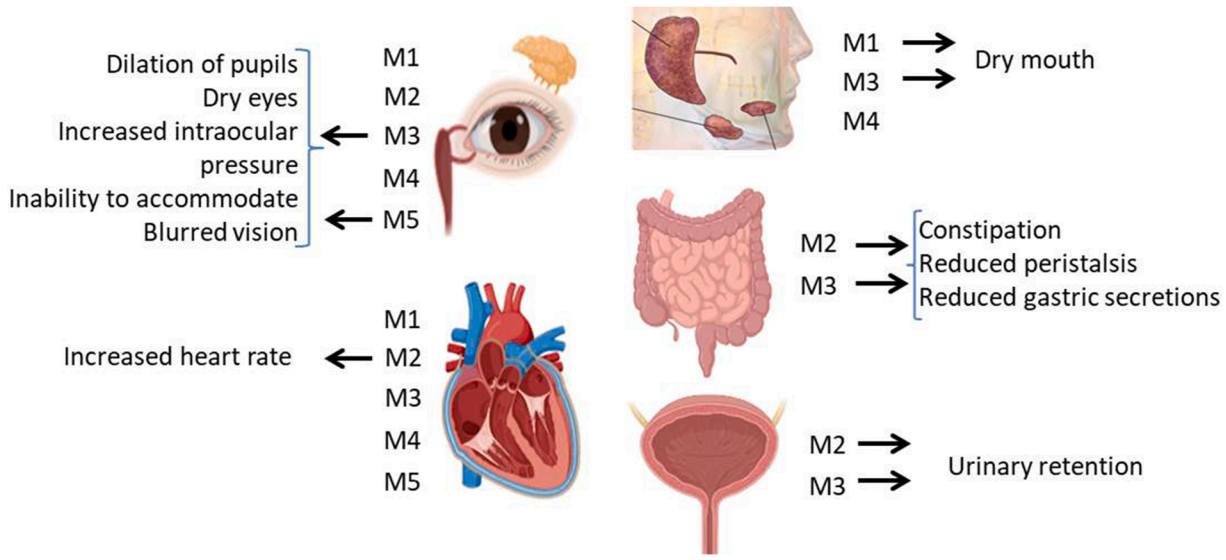

Fig. 2. Peripheral adverse effects of muscarinic antagonism.

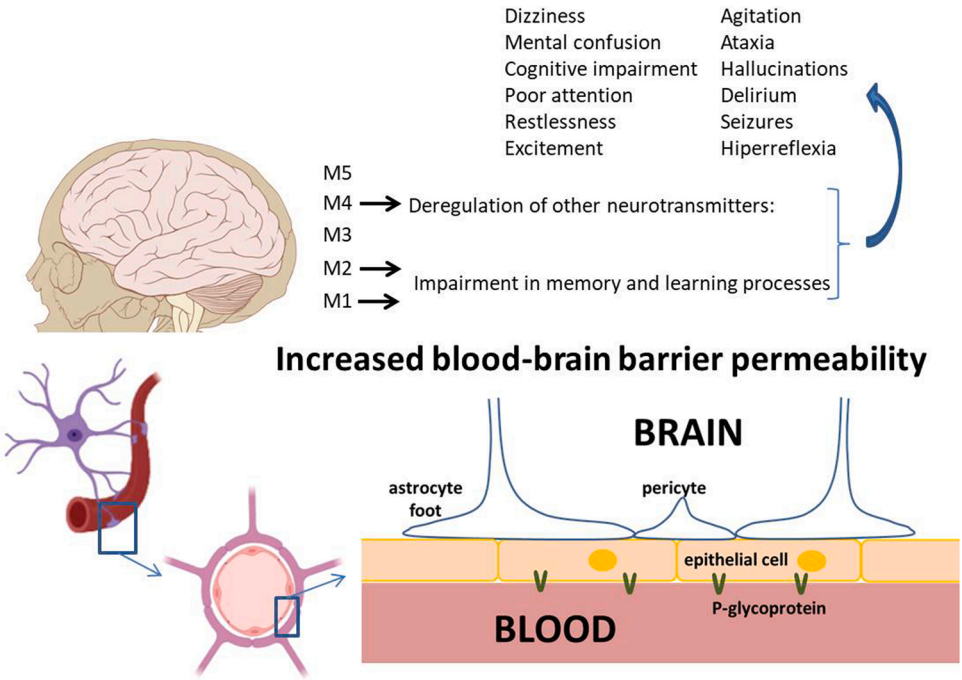

Fig. 3. Central adverse effects of muscarinic antagonism.
Antagonism of M1 and M2 receptors leads to impairment in memory and learning processes [17,20]. The M1 receptor is the most prevalent subtype in the CNS and has a crucial role in mediating cholinergic effects on cognitive function [17], while M2 receptors participate in memory processing. M4 antagonism has an impact on the regulation of other neurotransmitters, such as dopamine. M3 antagonism does not affect behavior or cognition due to scarce distribution of these receptors in the CNS [20].

3.1. Peripheral adverse effects

Dry mouth is the most common peripheral adverse effect of anticholinergic drugs [1]. It is mostly mediated by antagonism of M1 and M3 receptors and may have an important impact on the quality of life of affected individuals. Patients with dry mouth can have difficulties in swallowing, chewing or speaking and can present with a burning mouth, halitosis, altered taste, glossitis, cracked and peeled lips, and oral candidiasis. Additionally, older adults with dry mouth have an increased likelihood of developing dental caries, even in the presence of good oral hygiene, and may have difficulties in fitting dental prostheses [23].

Dilation of the pupils, dry eyes, increased intraocular pressure, inability to accommodate, and blurred vision are also common peripheral anticholinergic adverse effects. Resulting mainly from inhibition of M3 and M5 receptor subtypes, these effects can impair near vision, increasing the risk of falls and, consequently, decreasing functionality as well as exacerbating or precipitating narrow-angle glaucoma in predisposed patients [1,24].

In the gastrointestinal tract, constipation and reduced peristalsis are common antimuscarinic adverse effects that are mostly derived from antagonism M2 and M3 receptors [1,5,15,25]. In severe cases, this can lead to fecal impaction, altered absorption of concomitant drugs, and paralytic ileus [19]. Reduced gastric secretions can also occur [24].

Urinary retention, mediated by M2 and M3 antagonism, represents another common anticholinergic adverse effect, that occurs by parasympathetic pathway blockage, which impairs detrusor muscle contraction [5,19,24–26]. This effect is particularly relevant in patients with benign prostatic hyperplasia, increasing their risk of acute urinary retention [24].

Increased heart rate is an anticholinergic adverse effect that mostly results from the blockade of M2 receptors [1,15,19,27]. This effect worsens the prognosis of patients with angina pectoris [24]. Conduction

disturbances or supraventricular tachyarrhythmia can also occur in severe cases [24].

3.2. Central anticholinergic adverse effects

Central anticholinergic adverse effects result from the inhibition of ACh transmission in particular regions of the brain: the cerebral cortex, forebrain, corpus striatum and hippocampus (Fig. 3) [1]. The most frequent central adverse effects range from drowsiness, dizziness, lightheadedness, mental confusion, mild amnesia, cognitive impairment, poor attention, restlessness, inability to concentrate, and excitement to more serious effects such as agitation, disorientation, ataxia, hallucinations, delirium, seizures, and hyperreflexia [1,5,15,19,25].

3.3. Pharmacokinetics and pharmacodynamics of anticholinergic adverse effects

Older people are more sensitive to the anticholinergic adverse effects due to physiological changes typical of the aging process [1]. Those differences have an impact on pharmacokinetic and pharmacodynamic mechanisms that, in association with other age-related factors (*e.g.*, polypharmacy, drug-drug interactions, individual characteristics), favors anticholinergic adverse effects [18].

Central anticholinergic adverse effects result from the distribution of drugs with anticholinergic activity into the CNS and the competitive binding affinity of these drugs to muscarinic receptors. Factors that influence blood–brain barrier (BBB) permeability and the molecular characteristics of drugs are important to establish the risk of central adverse effects. Molecular characteristics such as size, polarity and lipophilicity lead to different BBB permeabilities [20]. For instance, trospium chloride, a highly polarized quaternary amine, does not cross the BBB, while oxybutynin, a lipophilic tertiary amine, penetrates the BBB.

An augmented BBB permeability is an age-related physiological modification (Fig. 3). Mechanisms involved in this increased permeability include epithelial shrinkage, opening of tight junctions, and blood vessel dilation, which allow larger particles and polarized molecules to cross the BBB into the CNS [20,28]. Additionally, the occurrence of certain clinical conditions, which are highly prevalent in older adults, such as neurodegenerative diseases and diabetes [20,29], or the use of some drugs such as lansoprazole, omeprazole, loperamide, simvastatin, clonidine or methyldopa also increase BBB permeability [19].

Cerebral P-glycoprotein function also decreases with aging (Fig. 3). Subsequently, older people using drugs with anticholinergic activity that are substrates of this efflux protein (eg. trospium chloride and darifenacin) are at increased risk of having central anticholinergic toxicity [1,17,19]. Aging is also accompanied by increased pharmacodynamic sensitivity to CNS muscarinic receptor blockage [20] resulting from a reduction in cholinergic reserves in the aging brain and a structural change in the muscarinic binding sites that has impact on the ACh binding affinity [18,20]. It has also been described that there is a reduction in the activity of the presynaptic choline acetyltransferase, which reduces the levels of ACh in the CNS, and a lower muscarinic receptor density [20].

Patients with Alzheimer's disease (AD) are more vulnerable to central anticholinergic effects because they have a serious impairment in cholinergic neurotransmission, a decrease in the number of cholinergic neurons, ACh receptors dysfunction, and signaling dysregulation as well as a compromised BBB that favors the penetration of drugs into the CNS [17–19,30]. Additionally, people with the ε4 allele of apolipoprotein E (APOE ε4), a major genetic risk factor for AD, have an increased cognitive sensitivity to drugs with anticholinergic activity [17,31].

4. Methods used to measure the anticholinergic burden

Anticholinergic burden is defined as the cumulative effect of using one or more drugs with anticholinergic activity [1,14,25,27,32,33]. No agreement on how to measure anticholinergic burden exists [34]. The most important methods for quantifying anticholinergic activity include:

- Measuring drug affinity for muscarinic receptors, as evaluated by *in vitro* studies through the equilibrium dissociation constant [18];
- Determination of serum anticholinergic activity, as measured by a radioreceptor assay [35];
- Brain imaging of muscarinic receptors using a high-affinity muscarinic receptor antagonist during single-photon emission computed tomography [18];
- Pretabulated scoring tools.

4.1. Serum anticholinergic activity

Serum anticholinergic activity (SAA) was considered the gold standard in the quantification of anticholinergic burden [1,19]. SAA is the most frequently used laboratory technique to measure anticholinergic activity [19]. In the early 1980s, Tune and colleagues [35] developed a radioreceptor assay to quantify an individual's overall anticholinergic burden originated by the cumulative effect of the drugs used, their metabolites, and other unknown endogenous factors [32]. The bioassay consisted of assessing the competitive binding of a strong antimuscarinic compound and the serum of a patient treated with anticholinergic drugs [17]. The tritiated radioligand quinuclidinyl benzilate (^{3}H-QNB) was selected because of its high and specific affinity for all the muscarinic receptor subtypes (M1-M5). Anticholinergic drugs competitively inhibit ^{3}H-QNB binding to the muscarinic receptors obtained from a homogenate of rat forebrain. The displacement of ^{3}H-QNB bound is used to quantify SAA. Atropine is used to develop the standard curves, and the results of SAA are expressed in picomoles of atropine equivalents per milliliter (pmol/mL). The results range from the lowest detectable limit of 0.25 pmol/mL to 25.00 pmol/mL [1,16,32].

In 2008, Chew and colleagues used SAA in a study that aimed to measure the anticholinergic activity of 107 drugs commonly used by older people to inform clinicians on how to reduce the anticholinergic burden by prescribing equally efficacious drugs [4,20]. From the 107 drugs studied, 39 had detectable anticholinergic activity, with 22 presenting dose-dependent anticholinergic activity (*e.g.*, citalopram, amitriptyline, tolterodine), whereas 17 showed anticholinergic activity only at the highest doses (*e.g.*, digoxin, diazepam, furosemide). Chew, et al. reported that up to 90 % of older community-dwelling adults have detectable SAA [4]. A limitation attributed to this study was the fact that only parent drugs and not their metabolites were studied, ignoring the potential anticholinergic activity of these metabolites. For instance, clozapine, oxybutynin and tolterodine were tested in the study as active substances, but their metabolites that are known to bind to muscarinic receptors were not evaluated [17]. Subsequently, several studies measured the anticholinergic activity of many drugs using SAA, and many drugs with no expected anticholinergic activity demonstrated the ability to displace ^{3}H-QNB from the muscarinic receptors [20].

Several studies reported an association between SAA and low cognitive abilities (*i.e.*, cognitive impairment, delirium, impaired self-care capacity, and verbal memory) [1,20,36–38] and with functional impairment (*i.e.*, impairment in activities of daily living) [32]. SAA is commonly accepted as a biomarker for cognitive and functional impairment in older people [32]. However, the validity of SAA as a biomarker is controversial [32]. In reality, SAA reflects the activity of peripheral circulating anticholinergic compounds, but it does not reflect activity in the CNS since peripheral SAA levels may not be correlated with levels obtained in the brain [1,5,20,32]. Consequently, no definite threshold of SAA to predict delirium or cognitive dysfunction has been established [32,34]. The prediction of central anticholinergic burden should take into consideration the level of brain distribution of the drug

[20]. The misleading [13] information provided by SAA is patent among the spasmolytic drugs used for urinary incontinence. Oxybutynin presented low anticholinergic activity when compared to other spasmolytic drugs, but clinical studies have shown that oxybutynin may cause cognitive impairment probably due to high brain distribution [20]. Conversely, M3 selective antagonists, such as darifenacin, may have high SAA but minimal CNS effects due to low levels of this receptor subtype centrally [16]. Measuring the anticholinergic activity in cerebrospinal fluid could give a better estimate of the anticholinergic burden in the CNS, but it still would not predict individual sensitivity since it would not consider brain drug distribution [5,20]. Gerretsen and Pollock suggested the use of human cloned selective muscarinic receptor subtypes (*e.g.*, M1 subtype) to enhance the specificity and reliability of the bioassay to predict CNS effects [16].

In addition, SAA does not distinguish between the anticholinergic activity originating from anticholinergic drugs, endogenous compounds, or stress responses to acute illnesses [5]. It has been demonstrated that SAA increases during acute illness and declines after recovery [39]. Additionally, there are natural substances, such as cortisol, that have binding affinity to muscarinic receptors *in vitro* [20]. Furthermore, plasma proteins can interfere with binding of ^{3}H-QNB in the bioassay and, consequently, interfere with SAA results [16,20]. In consequence, SAA only indicates that a patient's serum contains compounds that affect binding to one or more muscarinic receptor subtypes [17,20]. However, this bioassay does not differentiate between intrinsic and extrinsic SAA [1].

A third limitation of SAA is the nonspecific affinity of ^{3}H-QNB, which binds to all muscarinic receptor subtypes, impeding the identification of different drug affinity patterns for each receptor subtype [1,5,20]. However, the bioassay may be less sensitive to substances that preferentially bind to M3 or M5 because rat brain homogenate is predominantly composed by M1, M4 and, to a lesser extent, M2 subtypes [4]. As M1 receptors have a major role in cognitive function, studies regarding cognition could be more accurate if only the influence of this subtype is considered [13].

Several other limitations to the use of SAA as a gold standard have been noted. SAA does not differentiate between antagonistic and agonistic binding to muscarinic receptors [5,19,20]. It also does not assess the effects of drug metabolites, such as N-desmethylclozapine [19]. Furthermore, methods used to perform the SAA test vary between different laboratories, which results in a wide dispersion of the values reported among the various studies [1,5,16,20]. This heterogeneity may be associated with the use of different models to calculate atropine standard curves as the reference for anticholinergic activity [20]. The complexity of using the SAA procedure is also associated with its cost, applicability, and feasibility in clinical practice. In fact, it is a method that is not readily available, and sometimes it is hard to interpret. Finally, the measurement of total SAA does not provide guidance regarding which drug with anticholinergic activity should be discontinued [1].

To improve the validity of the SAA bioassay, Nobrega and colleagues have proposed modifications to the original method. The main variations include the use of cells expressing only M1 receptors as opposed to rat brain tissue and the use of a perchloric acid pretreatment to neutralize potential effects of endogenous proteins in serum samples [40].

4.2. Anticholinergic burden scales and indexes

The limitations of the SAA method and the attempts to improve anticholinergic risk stratification have stirred the development of a different approach to assess anticholinergic burden: anticholinergic burden scales and indexes. These tools aim to give clinicians a practical guide to identify drugs with anticholinergic activity, quantify anticholinergic burden, and anticipate anticholinergic adverse effects [1,13,25]. Cardwell defined the key attributes of an ideal anticholinergic risk tool: it has to be an evidence-based tool that is concise and easy-to-use, show an association with clinical outcomes, provide an indication of severity/risk, achieve good interrater reliability, offer alternatives to improve anticholinergic prescriptions, be regularly updated, and have an international scope, but it should also be feasible to use in computerized clinical decision support systems [25]. In general, anticholinergic burden tools classify drugs with anticholinergic activity into 3–5 ranking levels, ranging from no anticholinergic activity (assigned score 0) to high/definite anticholinergic activity (assigned scores 3, 4 or 5) [41]. The total anticholinergic burden is calculated by adding the scores given to each drug. Different systematic reviews have identified many anticholinergic burden scales and indexes [13,14,41]. They all differ in their origin, content, and how they quantify the anticholinergic activity of included drugs [41]. Table 1 presents the characteristics of anticholinergic burden scales and indexes gathered after a comprehensive literature review.

4.2.1. Clinician-rated Anticholinergic Score (CrAS)

The CrAS was developed in the U.S. in 2001 by Han et al. within a study that aimed to evaluate the association between the use of drugs with anticholinergic activity and the severity of delirium symptoms in a cohort of 278 patients diagnosed with delirium [42]. Originally, the authors established a list of 340 drugs including drugs used by the study population and other drugs reported in the literature as having anticholinergic effects. Then, 3 experts independently rated the anticholinergic effect of each drug from 0 (none) to 3 (high) based on their clinical experience and knowledge of anticholinergic properties. Finally, authors assessed the interrater reliability between the 3 expert ratings for all the 340 drugs as well as the concordance of the mean and the median values with Summers' list of drugs that can induce delirium [61] and 3 different sources of laboratory data. Later, in 2008, Han et al. modified the list to create a reduced version based on the old CrAS [43]. The new CrAS was developed as a 4-point scale (0−3) and included only 60 drugs selected from the first version through an expert panel opinions; this system was tested in a cohort study with 2 years of follow-up that included a total of 544 hypertensive men aged older than 65 years. The outcomes studied were memory performance and executive function.

4.2.2. Anticholinergic Burden Score (ABS)

The ABS was created in 2002 by Aizenberg in Israel [44]. A 4-year case-control study was conducted including elderly psychiatric inpatients with the aim of establishing an association between the use of drugs with anticholinergic activity and the risk of falls. The ABS was created as a summative score by including the drugs that were found to be associated with individuals who had fallen in the study. The ABS classified these drugs with a 6-point scale (0−5), where a score of 0 corresponds to no anticholinergic effect, and a score 5 corresponds to high anticholinergic effects. These scores were attributed in accordance to data previously published by Shiloh and colleagues [62]. Unfortunately, as reported by several authors, Aizenberg et al. have never reported the entire list [13].

4.2.3. Clinical index and pharmacological index

In 2004, in the U.S., Minzenberg and colleagues conducted a cross-sectional study that included 106 outpatients with schizophrenia [45]. They aimed to establish a clinically relevant standard index of the relative anticholinergic potency of psychiatric medications as well as to assess the association between anticholinergic burden and cognitive function impairment (low attention and memory) in patients with schizophrenia. The authors created two different indexes: a clinical index and a pharmacological index. The clinical index was created by a panel of 10 experts with extensive experience in clinical psychopharmacology who independently rated the clinical potency of each drug (scoring range: 1−228), with reference to 1 mg of oral benztropine mesylate, based on patient complaints of dry mouth, blurred vision, and

Table 1
Characteristics of the Anticholinergic burden scales and indexes.

Anticholinergic burden tool	Local, year (Author)	Original study (design and population)	Outcomes studied	Scoring range	Scoring criteria	Number of drugs
Clinician-rated Anticholinergic Score (CrAS)	USA, 2001 Last update: 2008 (Han) [42] [43]	Prospective cohort Community	Cognitive function Functional outcome	0-3	-Literature review -Laboratory data -Expert opinion -Summer's Drug Risk Number	60
Anticholinergic Burden Score (ABS)	Israel, 2002 (Aizenberg) [44]	Prospective Hospital	Falls	0-5	-Anticholinergic effects of psychotropic drugs -Previous data published by Shiro et al.	Not reported
Clinical Index (CI)	USA, 2004 (Minzenberg) [45]	Cross sectional Outpatients with schizophrenia	Cognitive function (attention and memory)	1-228 (benztropine equivalents)	-Anticholinergic effects of drugs -Literature review -Expert opinion	21
Pharmacological Index (PI)	USA, 2004 (Minzenberg) [45]	Cross-sectional Outpatients with schizophrenia	Cognitive function (attention and memory)	0.7-1470 (benztropine equivalents)	-Literature review -Receptor binding -Effects of anticholinergic drugs on neurocognitive or neuropsychological function	24
Anticholinergic Drug Scale (ADS)	USA, 2006 (Carnahan) [46]	Cross-sectional Long-term care residents	SAA	0-3	-Previous published scale (CrAS) -Expert opinion	117
Anticholinergic Burden Classification (ABC)	France, 2006 (Ancelin) [47]	Longitudinal cohort study General practitioner outpatients	Cognitive function Mild cognitive impairment	0-3	-SAA -Literature review -Expert opinion	27
Drug Burden Index (DBI)	USA, 2007 (Hilmer) [48]	Cross-sectional Community-dwelling	Physical and cognitive performance	0-1	-Pharmacological model, with consideration of daily dose and minimum recommended daily dose -Mosby's Drug Consult and the Physicians' Desk Reference	-
Anticholinergic Risk Scale (ARS)	USA, 2008 (Rudolph) [49]	Retrospective and prospective cohort Hospital and long-term care	Anticholinergic adverse effects (peripheral and central)	0-3	-Literature review -Dissociation constant (pKi) for cholinergic receptor - Input into Micromedex (determination of anticholinergic adverse effects) -Expert opinion	49
Anticholinergic Cognitive Burden Scale (ACB)	USA, 2008 Last update: 2012 (Boustani) [50]	Review	Negative cognitive effects (delirium, MCI, dementia or cognitive decline)	0-3	-Literature review -SAA and *in vitro* affinity to muscarinic receptors -Expert opinion	99
Chew's list	USA, 2008 (Chew) [4]	*In vitro* study	Anticholinergic activity *in vitro*	0-4	-SAA	107
Cancelli's Anticholinergic Burden Scale	Italy, 2008 (Cancelli) [51]	Retrospective Outpatients with dementia	Psychosis	0-3	-Literature review - *In vitro* anticholinergic activity -Published data about anticholinergic effects -Expert opinion	17
Anticholinergic Activity Scale (AAS)	Norway, 2010 (Ehrt) [52]	Longitudinal prospective cohort Community patients with Parkinson disease	Cognitive function	0-4	-Chew's list -SAA -Literature review -Expert opinion	29
Anticholinergic Loading Scale (ACL)	Australia, 2011 (Sittironnarit) [53]	Cross-sectional Community-dwelling	Cognitive function	0-3	-CrAS -SAA -Expert opinion	49
Whalley's Anticholinergic Burden Scale	UK, 2012 (Whalley) [54]	Longitudinal observational Community-dwelling	Cognitive function	0-3	-Ancelin's scale -Literature review -Expert opinion	62
Durán's list	Ecuador, 2013 (Durán) [27]	Systematic review of previously published anticholinergic burden scales	-	Low and high potency	-ADS, ABC, CrAS, ARS, Chew's list, AAS and ACL - Martindale®	100
Drug Burden Index – World Health Organization	International, 2014	Longitudinal observational cohort	Mortality	0-1		-

(*continued on next page*)

Table 1 (*continued*)

Anticholinergic burden tool	Local, year (Author)	Original study (design and population)	Outcomes studied	Scoring range	Scoring criteria	Number of drugs
(DBI-WHO)	(Dauphinot) [55]	Hospital			-DBI (replacing minimum recommended daily dose by defined daily dose)	
Composite rating scale	New Zealand, 2015 (Salahudeen) [14]	Systematic review of previously published anticholinergic burden scales	-	Low, moderate and high potency	- ADS, ABC, CrAS, ARS, ACB, AAS and ACL	195
Non-linear Pharmacological binding model	New Zealand, 2015 (Salahudeen) [56]	Retrospective population-level Hospital	Delirium, constipation, urinary retention	-	-Drugs' binding to receptor -Patients' characteristics -Salahudeen's scale	-
Muscarinic Acetylcholinergic Receptor ANTagonist Exposure (MARANTE)	Belgium, 2016 (Klamer) [57]	Longitudinal cohorts Community- dwelling and nursing home residents	-	Potency: 0-2 Dosage ranges: 0; 0.5; 1; 1.5; 2	-Durán's list -Authoritative sources -Expert opinion	41
Anticholinergic Effect on Cognition (AEC)	UK, 2017 (Bishara) [58]	Review of literature	-	0-3	-Literature review - *In vitro* affinity to muscarinic receptors - Dissociation constant (pKi) for cholinergic receptor -Capacity to cross BBB -Reports of cognitive adverse effects -Expert opinion	122
Anticholinergic Burden Score for German prescribers	Germany, 2018 (Kiesel) [59]	Retrospective study Acute geriatric ward	-	0-3	-Literature review -Previously published scales: ADS, ABC, ARS, CrAS, AAS, ACL, ACB, Durán's list -German Summary of Product Characteristics and DRUGDEX® -Expert opinion	151
Brazilian scale	Brazil, 2019 (Nery) [59]	Review of literature	-	1-3	-Literature review -Previously published scales: ADS, ABC, CrAS, ARS, Chew's list, ACB, AAS, ACL, AEC, MARANTE and AIS -Beers Criteria 2015 -Martindale® -Expert opinion	125
Korean Anticholinergic Burden Scale (KABS)	Korea, 2019 (Jun) [60]	Review of literature		0-3	-Literature review -Previously published scales: ACB, ADS, ARS, ACL, CrAS, Chew's list, AAS, ABC -Beers Criteria 2015 -Strong anticholinergic medication lists suggested by Gray et al. -Expert opinion	494

SAA – Serum Anticholinergic Activity; MCI – Mild Cognitive Impairment; BBB – Blood Brain Barrier.

constipation. The pharmacological index was based on a literature review of studies addressing the effects of drugs with anticholinergic activity on neurocognitive or neuropsychological function, compiling a list of drugs with *in vitro* brain muscarinic receptor antagonism reported. Relative affinities for brain muscarinic receptors were typically reported as K_d values for the displacement of ^{3}H-QNB binding. The data were converted to relative benztropine equivalents based on the K_d for benztropine mesylate (scoring range: 0.7−1470). The total anticholinergic burden, expressed relative to 1 mg of benztropine mesylate, was calculated for each of the 106 patients by adding both indexes, clinical and pharmacological.

4.2.4. Anticholinergic Drug Scale (ADS)

The ADS was developed in the U.S. in 2006 by Carnahan and colleagues [46]. The ADS is a scale based on a cross-sectional study that included a total of 279 residents from long-term care facilities with a mean age of 86 years. This scale is based on the CrAS [42] and was initially referred as to as the CrAS modified version. An expert panel identified and reviewed 340 drugs with potential anticholinergic activity. The final scale comprises a total of 117 drugs classified in four levels: score 0 – no known anticholinergic properties; score 1 - drugs with potentially anticholinergic activity as evidenced by receptor binding studies; score 2 - drugs with anticholinergic adverse events, usually at excessive doses; and score 3 - drugs with marked anticholinergic properties. To validate the ADS, the authors assessed the association of the scores with SAA and reported a significant association.

4.2.5. Anticholinergic Burden Classification (ABC)

The ABC was created in 2006 in France [47]. Developed by Ancelin et al., the ABC is a 4-point scale (0−3) based on a literature review, SAA, and expert opinions. The ABC contains a total of 27 drugs, with scores assigned based on the route of administration, potential drug-drug interactions, and BBB permeability, but the dose is ignored. A score of 0 corresponds to no anticholinergic activity; a score of 1 indicates drugs with no likely anticholinergic activity; a score of 2 refers to drugs with low anticholinergic effects; and a score of 3 corresponds to drugs with

high anticholinergic effects.

4.2.6. Drug Burden Index (DBI)

The DBI was developed in 2007 by Hilmer and colleagues in the U.S. [48]. A cross-sectional study enrolling 3075 community-dwelling older people (aged 70–79 years) was conducted and aimed to examine the association between drug use and physical and cognitive performance. The DBI calculates exposure to both anticholinergic and sedative medications based on the principles of dose-response and maximal effect. The total DBI assumes the following equation:

$$\text{Total Drug Burden Index} = B_{AC} + B_S$$

where B_{AC} indicates the anticholinergic burden (or anticholinergic subscale – DBI-Ach), and B_S indicates the sedative burden (or sedative subscale – DBI-sedat). This pharmacological model assumes that the anticholinergic and sedative burdens of drugs are summative and linear rather than synergistic. Each of these two components is calculated with the following equation:

$$\text{Drug Burden Index} = \Sigma\, D/(\delta + D)w$$

where D is the daily dose taken by the patient, and δ is the dose required to achieve 50 % of the maximum effect (DR_{50}). Hilmer et al. recognized the difficulty of obtaining the DR_{50} of many drugs and suggested using the minimum recommended daily dose as an alternative. The equation results in a hyperbolic function ranging from 0 to 1 for each drug, where 0.5 indicates an exposure to a drug at its minimum efficacious dose. The authors identified medications with clinically significant anticholinergic or sedative effects by consultation of two commonly used drug compendia, Mosby's Drug Consult and Physicians' Desk Reference. Initially, the minimum recommended daily dose was established according to approved US Food and Drug Administration (FDA) information. Further studies using the DBI established the British National Formulary as the gold standard for obtaining this information [63].

4.2.7. Anticholinergic Risk Scale (ARS)

The ARS was developed in the U.S. in 2008 [49]. Rudolph et al. identified 500 of the most prescribed medications within Veterans Affairs Boston Healthcare system that were independently reviewed by 1 geriatrician and 2 geropharmacists who identified drugs with potential to cause anticholinergic adverse effects. Topical, ophthalmic, otologic and inhaled drugs were excluded. The drugs resulting from this literature review were then assessed in 3 different analyses: determination of the dissociation constant (pKi) for the cholinergic receptor; the anticholinergic adverse effects rates compared with placebo, obtained from Micromedex; and a literature review related to anticholinergic adverse effects. Finally, a 4-point scale (0−3) with a total of 49 drugs with anticholinergic activity was created. Drugs were then ranked by 0, 1, 2 or 3 points indicating limited or no anticholinergic potential, moderate, strong and very strong anticholinergic potential, respectively.

4.2.8. Anticholinergic Cognitive Burden Scale (ACB)

The ACB was first developed in the U.S. in 2008 by Boustani and colleagues [50], with a last update published in 2012 [64]. The ACB was created to be a practical tool that identifies the severity of anticholinergic effects on cognition of prescribed and over-the-counter drugs. The authors performed an extensive literature review of studies that measured drugs' anticholinergic activity and their association with cognitive function in older adults, specifically delirium, mild cognitive impairment, dementia or cognitive decline. From each study, the authors extracted the method used to evaluate anticholinergic activity and the list of medications that were associated with negative cognitive effects. The final list was presented to an expert panel who established the following scoring system: score of 1 – drugs with possible anticholinergic effects, as demonstrated by the SAA assay or *in vitro* affinity to muscarinic receptors but no clinically relevant negative cognitive effects; scores of 2 and 3 – drugs with established and clinically relevant cognitive anticholinergic effects based on the drug BBB permeability and its association with the development of delirium. All other drugs with no anticholinergic effects scored 0. The final scale was updated in 2012 and includes a total of 99 drugs.

4.2.9. Chew's list

The Chew's list was developed in 2008 by Chew and colleagues [4]. This list was created with the aim of measuring the anticholinergic activity of drugs more commonly used by older adults. The authors used the SAA radioreceptor assay to investigate the anticholinergic activity of 107 drugs *in vitro*. Additionally, they assessed six clinically relevant concentrations for each drug. When anticholinergic activity was detected, the average steady-state peak plasma and serum concentrations (C_{max}) in older adults were used to estimate the relationship between the doses used and anticholinergic activity. Potential CNS distribution was also evaluated for the drugs that demonstrated anticholinergic activity, with the following categorization: unknown status, none or minimal distribution, suspected or low distribution, and moderate or high distribution. This classification was based on what was expected in a healthy older adult. However, the authors noted that BBB permeability can be affected by some chronic diseases, acute viral or bacterial infections or concomitant medications. The anticholinergic activity of the 107 drugs was categorized into 5 levels: 0 – no anticholinergic activity at therapeutic doses; 1 – no or minimal anticholinergic activity (no anticholinergic activity at doses across the therapeutic range; however, patients with an above average C_{max} or those receiving supratherapeutic doses may show some activity); 2 – low anticholinergic activity (0.5−5 pmol/mL of atropine equivalents across therapeutic range); 3 – moderate anticholinergic activity (5−15 pmol/mL); and 4 – high anticholinergic activity (>15 pmol/mL).

4.2.10. Cancelli's Anticholinergic Burden Scale

Cancelli's scale was created in 2008 in Italy [51]. The authors aimed to investigate whether drugs with anticholinergic properties constitute risk factors for the development of psychosis in patients affected by Alzheimer's disease. Based on a literature review, published anticholinergic lists, previous studies dealing with anticholinergic effects and those reporting *in vitro* anticholinergic activity [3,65], Cancelli's scale included a total of 17 drugs. The drug dosage and route of administration were also considered. The classification of the drugs was presented according with the following scoring system: 0 – drugs with no anticholinergic effect; 1 – drugs with no likely anticholinergic effect; 2 – drugs with moderate anticholinergic effects; and 3 – drug with high anticholinergic effects.

4.2.11. Anticholinergic Activity Scale (AAS)

The AAS was developed in 2010 in Norway by Ehrt et al. [52]. The authors aimed to investigate the association between the use of drugs with anticholinergic activity and cognitive decline in a population of 235 patients with Parkinson's disease. The authors assessed the anticholinergic activity of all the 99 drugs used by the study population. Based on Chew's list, the authors created a 5-point scoring system (0−4). The drugs that were not included in Chew's study were evaluated by 2 of the authors who independently performed a literature review. As a result, the AAS includes 29 drugs with anticholinergic activity with no consideration of dose, and the drugs are ranked as follows: score of 0 - no anticholinergic activity; scores of 1, 2, 3 and 4 – no or minimal, low, moderate and high anticholinergic activity, respectively.

4.2.12. Anticholinergic Loading Scale (ACL)

The ACL was developed in Australia in 2011 by Sittironnarit et al. [53]. It is a 4-point scale (0−3) based on previous published methods used to assess anticholinergic activity (SAA and clinician-rated scores) and expert opinion [66]. When data were available, drugs were assigned an already published score. In the case of drugs that had not been

previously classified, the authors applied a classification (0−3) based on an independent rating by a 4-expert panel. A score of 0 indicates no anticholinergic effect, and a score of 3 indicates a strong anticholinergic effect. The ACL resulted in a list of 292 drugs, of which 49 have at least some anticholinergic activity, with no consideration of dose.

4.2.13. Whalley's scale

Whalley's scale was developed in 2012 in the UK [54]. It is a 4-point scale (0−3) based on a literature review, a previous anticholinergic scale (Ancelin et al.) [47], and expert opinion. The classification of the anticholinergic effects of drugs was performed independently by two of the authors according to the following criteria: score 0 – no drugs used; score 1 – drugs used but with no likely effect; score 2 – drugs used with a low effect; and score 3 - drugs used with a high effect. The scale includes a total of 62 drugs with some anticholinergic effect, and the duration of exposure was considered.

4.2.14. Durán's list

Durán's list was developed in 2013 [27]. It was created by a systematic review of previously published anticholinergic scales with the aim of creating a uniform list of drugs with anticholinergic activity. After the systematic search, seven anticholinergic risk scales were included: Chew's list, the ADS, ABC, CrAS, ARS, AAS and ACL. For all scales, quantitative grading scores were extracted. In cases of discrepant scores between scales, the authors used information contained in Martindale's The Complete Drug Reference to support the final decision. A total of 225 drugs were evaluated, and 100 drugs were included in the list as having clinically relevant anticholinergic activity: 47 drugs were classified as having high anticholinergic potency, and 53 drugs were classified as having low potency.

4.2.15. Drug Burden Index – World Health Organization (DBI-WHO)

The DBI-WHO was developed in 2014 as an attempt to create a standard international version of the DBI [67]. Faure and colleagues considered that international comparison of DBI scores was difficult because dosages and indications could vary between countries; thus, δ should be constantly redefined according to local context. To overcome this limitation, the authors proposed to use a common δ for the DBI calculation, suggesting the defined daily dose (DDD), representing the average maintenance dose per day for a drug used for its main indication in adults, as defined by the WHO. However, the original creators of the DBI did not agree with this approach, arguing that the DDD is not related to a drug's DR_{50} and that δ should be an estimate of this pharmacological parameter [68].

4.2.16. Salahudeen's scale

In line with what was developed by Durán, Salahudeen's scale is also the result of a systematic review of previous published scales [14]. Conducted in 2015, this work aimed to create a standardized list of drugs with anticholinergic activity based on pre-existing scales – the ADS, ABC, CrAS, ARS, ACB, AAS and ACL. Drugs with anticholinergic activity described in the 7 scales were collected into a uniform list that the authors named a "composite rating scale to categorize anticholinergic activity medicines". This scale comprised 195 drugs classified as having low, moderate or high anticholinergic activity.

4.2.17. Non-linear pharmacological binding model

In 2016, Salahudeen et al. [56] conducted a study that aimed to investigate the influence of patients' characteristics on the occurrence of anticholinergic-type effects. Based on the need to explore the effect of anticholinergic events using non-linear models, authors considered the following patients' characteristics: medicines with anticholinergic effects according to Salahudeen's scale (ACh burden), age, sex, non-anticholinergic medicines (non-ACM), Charlson comorbidity index scores, ethnicity, and number of hospital admissions during the study period. Anticholinergic-type effects included delirium, constipation, and urinary retention. This non-linear model considers drugs' binding to receptor and explored whether patients' characteristics increased the risk of events independent of ACh burden (*i.e.* they pose a risk even in the absence of ACh burden), increased the maximal anticholinergic effect of ACh burden (*i.e.* an overall greater effect is seen with ACh burden), and increased the apparent potency of the ACh burden (*i.e.* greater effects were seen for a given ACh burden value). The results showed that ACh burden was an independent risk factor to predict the probability of anticholinergic-type events in older people.

4.2.18. Muscarinic Acetylcholinergic Receptor ANTagonist Exposure (MARANTE) scale

The MARANTE scale was developed by Klamer and colleagues in Belgium and published in 2017 [57]. The authors aimed to develop a new scale including the principles of potency and dose for the quantification of anticholinergic exposure in older adults. Information regarding potency was retrieved from Durán's list, and a score of 1 was assigned for low anticholinergic potency, while a score of 2 was assigned for high anticholinergic potency. Three different dose concepts were established for each drug identified in Durán's list and for all the drugs with anticholinergic activity used by two Belgian cohorts of older people as follows: a) (Geriatric) Minimal Effective Dose – (G)MinEV; b) (Geriatric) Maintenance Dose - (G)MainD; and c) (Geriatric) Maximal Effective Dose – (G)MaxEV. This dose information was established according to regulatory information sources and reviewed by an expert panel. The results obtained for different doses determined 4 dose ranges – low (0.5), moderate (1), high (1.5) and very high (2) – that were defined as follows:

- Low: Higher than zero (0 mg) and less than the (G)MinEV
- Moderate: Equal to or higher than the (G)MinEV but lower than the (G)MainD
- High: Equal to or higher than the (G)MainD but lower than the (G)MaxEV
- Very high: Equal to or higher than the (G)MaxEV.

The overall MARANTE score is calculated by the summation of each drug score, which is calculated by multiplying the potency score (1, 2) by the dosage range score (0.5, 1, 1.5, 2).

4.2.19. Anticholinergic Effect on Cognition (AEC)

The AEC was published in 2017, in UK, by Bishara and colleagues [58]. The authors aimed to develop a scale that focuses on the negative effect of drugs with anticholinergic activity on cognition. The authors identified drugs with anticholinergic activity and drugs associated with cognitive function among the most commonly used drugs by the elderly population. These drugs were investigated with the Ki database provided by the National Institute of Mental Health Psychoactive Drug Screening Program (PDSP), which contains the binding affinities (Ki) of drugs to muscarinic receptors. When available, information about M1 affinity was preferred, followed by M2 and M4 data, because these subtypes are more associated with cognitive impairment. This information as well as the BBB permeability of the drug was completed using other drug compendia and searches of bibliographic databases. A 4-point score based only on the anticholinergic activity was created:

- "Score 0: Ki>10 000 nM or published *in vitro* data showing no antimuscarinic activity or comment in Martindale or SmPC, stating no antimuscarinic effects";
- "Score 1: Ki 1001–10 000 nM or published *in vitro* data showing minimal or equivocal antimuscarinic action or comment in Martindale or SmPC, stating minimal, weak or mild antimuscarinic effects";
- "Score 2: Ki 100–1000 nM or published *in vitro* data showing moderate antimuscarinic effects or comment in Martindale or SmPC, stating some or moderate antimuscarinic effects";

- "Score 3: Ki<100 nM or published *in vitro* data showing strong antimuscarinic effects or comment in Martindale or SmPC, stating strong antimuscarinic effects".

Then, this score was refined according to the BBB permeability to the drug and its metabolites and the evidence published about central effects. Finally, 165 drugs were reviewed: 21 received a score of 3; 18 a score of 2; 21 a score of 1; and 62 a score of 0. Due to insufficient data, 43 drugs were not assigned any score.

4.2.20. Anticholinergic Burden Score for German prescribers

This scale was developed in 2018 by Kiesel and colleagues [59]. A PubMed search identified published systematic reviews of tools used to quantify anticholinergic burden. Three systematic reviews [25,27,33] containing 12 tools to quantify anticholinergic burden were identified, but only 8 scales were considered – Durán's list, the ADS, ABC, ARS, CrAS, AAS, ACL, and ACB. Topical, ophthalmic, otologic and nasal drugs were excluded. After excluding drugs not available in Germany, grading scores of drugs included in the scales were extracted, and the concordance criteria were applied to obtain a common score. Finally, an expert team established a final score. In addition to the drugs identified by the included scales, a retrospective evaluation of the medications used by 34 patients admitted to an acute geriatric ward was also performed. All drugs used by the study population at admission and discharge that were not mentioned in the reviewed scales were also assessed according to the methodology described for the above drugs requiring further evaluation. As a result, a total of 507 drugs were scored according to the following criteria: 356 scored 0 (no anticholinergic effects), 104 scored 1 (weak anticholinergic effects), 18 scored 2 (moderate anticholinergic effects), and 29 scored 3 (strong anticholinergic effects).

4.2.21. Brazilian Anticholinergic Activity Drug Scale

In 2019, Nery and colleagues developed this Brazilian scale [69]. Based on a literature review, the authors first identified 11 previously published anticholinergic burden scales: Chew's list, the ADS, ABC, CrAS, ARS, ACB, AAS, ACL, AEC, MARANTE and AIS. Drugs included in at least two previously published scales were considered. Then, the authors introduced drugs with known anticholinergic activity according to the ATC classification. Drugs with high anticholinergic activity mentioned in the 2015 Beers criteria were also added. Drugs used for ophthalmic diagnostic proposes and drugs not marketed in Brazil (according to the national authority – ANVISA) were excluded. Scores attributed to the included drugs ranged from 1 to 3, according to the previously published scales or, in cases of discrepancy, according to information from Martindale: The Complete Drug Reference. The final list included 125 drugs: 45 scored 3, 13 scored 2, and 67 scored 1.

4.2.22. Korean Anticholinergic Burden Scale (KABS)

This scale was created in 2019 by Jun et al. [60]. Authors aimed to develop a tool designed specifically for Korean healthcare system. First, a systematic review was performed to identify previously published anticholinergic burden tools. A composite list was created by extracting drugs and their scores from those identified tools (*i.e.*, ACB, ADS, ARS, ACL, CrAS, Chew's list, AAS and ABC). Additionally, medications included in 2015 Beers Criteria [70] and anticholinergic medication lists suggested by Gray et al. [71] were also considered. Drugs not available in Korea and topical drugs were excluded. Medications with the same fourth ATC level as those that were scored $\geq$1 from any list that were available in the Korean national reimbursement formulary were added. For medications with conflicting anticholinergic scores between lists or no anticholinergic score, a final score was determined after a literature review and expert consensus through a two-round Delphi process. The final list included 494 drugs: 56 scored 3, 23 scored 2, 59 scored 1, and 356 scored 0.

Anticholinergic burden scales and indexes have several strengths. These scoring systems allow determination of anticholinergic burden and identification of patients who are at particular risk of having anticholinergic adverse effects [17]. Therefore, these tools can serve as educational tools for prescribers and pharmacists since they can be used to anticipate anticholinergic adverse effects [27] and identify patients who will benefit from a medication review [17]. Additionally, they are objective, reproducible, and easy to use. They can also be applied in a short time, particularly if they are incorporated in computerized clinical decision support systems [19]. Another important factor is the fact that anticholinergic burden tools have already proven their association with important clinical outcomes [13,14,33,72].

Anticholinergic burden scales and indexes have a number of limitations. In the construction of many of them, the pharmacological mechanisms of muscarinic antagonism were extremely simplified. These tools do not differentiate possible agonistic or antagonistic binding, the different affinities for muscarinic receptors [33], and the potential development of tolerance effects over time. Additionally, these tools ignore potential synergistic or antagonistic drug-drug interactions, and few have considered differential BBB permeability, which are both characteristics of aged people commonly under polypharmacy. Moreover, muscarinic effects are dose dependent, and scales do not consider doses in their scoring systems. Furthermore, scales tend to assume that anticholinergic burden is linear and summative, while these effects are unlikely scalar [1,33,34]. Considering the finite number of muscarinic receptors, a plateau effect is expected, which implies that the summation of individual drug scores may overestimate the total anticholinergic burden in a patient [19]. Finally, anticholinergic burden scales are constituted by lists of drugs, which may rapidly be out of date and not applicable in other countries with different marketed drug portfolios. The DBI tried to solve some of these limitations by creating an index instead of a scale based on a list of drugs. The DBI considers the dose in the calculation and allows using updated drug compendia to identify the minimum recommended daily dose.

Previous studies have assessed the concordance among anticholinergic scales. Lertxundi and colleagues [73] evaluated the agreement among the ADS, ARS and ACB and concluded that there was poor agreement between the scales. Pont et al. [74] aimed to investigate the agreement among the ADS, ARS, ACB and the anticholinergic subscale (DBI-Ach) in a cohort of community-dwelling older men, and they found good agreement between the ACB and ADS (Cohen's kappa = 0.628, 95 % CI 0.593, 0.664), but poor agreement between the other tools (k = 0.091−0.264). Naples et al. [75] conducted a study to compare the concordance among the same four tools, and the results revealed low to moderate concordance among them (kappa ranged from 0.33 to 0.68).

4.3. Anticholinergic burden and anticholinergic adverse outcomes

Anticholinergic burden scales and indexes were created to help clinicians and other healthcare professionals to increase medication safety in older patients by predicting the occurrence of anticholinergic adverse effects. Although some studies concluded that these tools are associated with at least one adverse outcome [41], many other studies were not conclusive.

4.3.1. Cognitive outcomes

Adverse cognitive effects of drugs with anticholinergic activity have been assessed in several studies, mainly cross-sectional and longitudinal studies, in healthy patients, subjects with mild cognitive impairment, and patients with dementia [19], demonstrating a plausible association between cholinergic deficits and aging and associating them with the pathophysiology of dementia [5] (Table 2). However, evidence regarding the association between the use of drugs with anticholinergic activity and cognitive impairment is controversial. In addition, whether these effects are reversible or not is still unclear [32].

Ancelin et al. [47] assessed the association between the anticholinergic burden scale and nondegenerative mild cognitive impairment in elderly people and found that elderly people with a brief exposure to

Table 2
Association between Anticholinergic burden scales and indexes and cognitive outcomes.

Anticholinergic burden scale/ tool	Study	Setting and population	Outcomes studied	Association
Clinical Index and Pharmacological Index	Minzenberg, 2004 [45]	Cross-sectional Outpatients with schizophrenia	Simple attention	–
			Complex attention	+
			Short-term memory	+
			Delayed recall	+
			Semantic memory	+
			Working memory	–
			Executive functions	–
			Declarative memory	+
Clinician-rated Anticholinergic Scores	Han, 2001 [42]	Longitudinal observational Hospital	Delirium symptoms	+
			Dementia diagnosis	–
	Han, 2008 [43]	Prospective cohort Community-dwelling	Cognitive function (short term memory)	+
	Yeh 2013 [76]	Prospective cohort Veteran dementia care home	Cognitive function (MMSE)	–
	Low, 2009 [77]	Longitudinal Community-dwelling	Cognitive function	+
	Juliebo, 2009 [78]	Prospective Hospital	Delirium	–
	Drag, 2012 [79]	Cross-sectional Hospital	Cognitive function	–
Anticholinergic Drug Scale	Kersten, 2013 [80]	RCT Nursing home residents	Cognitive function (CERAD Delayed recall and recognition and MMSE)	–
	Kersten, 2013 [81]	Cross-sectional Nursing home residents	Cognitive function (CERAD immediate recall, delayed recall and recognition; MMSE)	–
	Lampela, 2013 [82]	Cross-sectional Community	Cognitive function (MMSE, verbal skills)	+
	Kashyap, 2014 [83]	Longitudinal cohort Outpatients	Cognitive function (MMSE)	+
	Huang, 2012 [84]	Retrospective Database	Delirium	+
			Cognitive function	–
	Lampela, 2013 [82]	Cross-sectional Community	Cognitive function (MMSE)	+
	Pasina, 2013 [85]	Cross-sectional prospective Hospital	Cognitive function (Short Blessed Test)	+
Anticholinergic Risk Scale	Bostock, 2013 [86]	Observational prospective Hospital	Cognitive function (Abbreviated Mental Test)	–
	Zimmerman, 2014 [87]	Cross-sectional Inpatients (palliative)	Delirium	+
	Landi, 2014 [88]	Cohort Nursing homes	Delirium	+
	Kashyap, 2014 [83]	Longitudinal cohort Outpatients	Cognitive function (MMSE)	+
	Campbell, 2010 [89]	Longitudinal Community-dwelling	Cognitive function	+
	Campbell, 2011 [90]	Observational cohort Hospital	Delirium	–
	Fox, 2011 [91]	Longitudinal Cohort Nursing homes, day hospital and inpaients (with Alzheimer disease)	Cognitive function (MMSE; Severe Impairment Battery)	–
	Fox, 2011 [2]	Longitudinal cohort Community-dwelling and institutionalized participants	Cognitive function	+
Anticholinergic Cognitive Burden Scale	Cai, 2013 [92]	Retrospective cohort Primary care clinic	Cognitive function (Mild cognitive impairment)	+
	Koyama, 2013 [93]	Longitudinal cohort Community-dwelling	Cognitive function (Mild cognitive impairment)	+
	Koyama, 2014 [94]	Prospective Community-dwelling	Cognitive function (MMSE)	–
	Pasina, 2013 [85]	Cross-sectional prospective Hospital	Cognitive function (Short Blessed Test)	+
	Shah, 2013 [95]	Cohort Community-dwelling	Cognitive function	+
	Kashyap, 2014 [83]	Longitudinal cohort Outpatients	Cognitive function	+
	Hilmer, 2007 [48]	Cross-sectional Community-dwelling	Attention, concentration (Digit Symbol Substitution Test)	+
Drug Burden Index	Best, 2013 [96]	Cross-sectional Hospital	*Delirium*	+
	Gnjidic, 2012 [97]	Cross-sectional Community-dwelling	Cognitive function	–
Drug Burden Index –Anticholinergic subscale	Cao, 2008 [98]	Cross-sectional Community-dwelling	Cognitive function (MMSE)	+
	Bostock, 2013 [86]	Observational prospective	Cognitive function (Abbreviated Mental Test)	–

(*continued on next page*)

Table 2 (*continued*)

Anticholinergic burden scale/ tool	Study	Setting and population	Outcomes studied	Association
Anticholinergic Activity Scale	Ehrt, 2010 [52]	Hospital Longitudinal cohort Community-dwelling (with Parkinson Disease)	Cognitive function (MMSE)	+
Anticholinergic Burden Classification	Ancelin, 2006 [47]	Longitudinal Nursing home residents	Mild cognitive impairment (Stockholm consensus group)	+
Anticholinergic Loading Scale	Sittironnarit, 2011 [53]	Cross-sectional Community (with Alzheimer disease)	Psychomotor speed and executive function	+
Cancelli's Anticholinergic Burden Scale	Cancelli, 2008 [51]	Retrospective Outpatients with Alzheimer disease (dementia centre)	Psychosis	+
	Cancelli, 2008 [99]	Cross-sectional Community	Cognitive function (MMSE) and Global Deterioration Scale	+
Chew's list	Lampela, 2013 [82]	Cross-sectional Community-dwelling	Cognitive function (MMSE and short distance vision)	+
	Jessen, 2010 [100]	Cohort Community-dwelling	Dementia Risk	+
Whalley's Anticholinergic Burden Scale	Whalley, 2012 [54]	Longitudinal observational Community-dwelling	Cognitive function (MMSE and visual attention) Developing dementia	+ –

MMSE – Mini-Mental State Examination; RCT – Randomized controlled trial.

drugs with anticholinergic activity had significant deficits in cognitive functioning and were highly likely to be classified as mildly cognitively impaired, although the risk of dementia had not increased. Cai et al. [92] found an association between anticholinergic burden, as measured by the ACB, and the risk of developing cognitive impairment, but only when high anticholinergic burden and prolonged exposure existed. In a large cohort study with 1304 older individuals, Fox et al. found that the ACB score was associated with an increased risk of cognitive decline, as measured by the Mini-Mental State Examination (MMSE), over 2 years in participants with normal or mildly impaired cognition [2].. Sittironnarit et al. [53] found an association between ACL scores and slower psychomotor speed or impaired executive function in a group of healthy controls [53]. However, they found no association between ACL scores and MMSE scores, memory and learning, attention and concentration, language skills, visuospatial skills, or any cognitive measures in mild cognitive impairment and Alzheimer's disease groups.. The CrAS presented conflicting results [42,76,43].. The results of the 6 studies evaluating ADS scores and cognitive function are also conflicting, with 3 studies reporting an association [77,82,83] and 3 reporting no association [79–81]. Among the 5 studies evaluating the ARS, 3 presented an association [82,83,85], and the other two showed no association with cognitive function [84,86]. Regarding the ACB, a total of 9 studies evaluated the association between the scale's scores and cognitive function, with 7 showing an association [2,83,85,89,92,93,95] and 2 showing no association [91,94]. In a retrospective 1-year follow-up longitudinal study with 1123 older hospitalized patients from acute care wards, Brombo et al. [101] found that patients with ARS scores of 1 or higher had significantly lower MMSE scores at discharge and a significantly greater decline in MMSE scores (-0.15/month) during follow-up. Similarly, patients with ACB scores of 1 or higher at discharge had a three-fold increased risk of developing a disability [101]. Regarding the DBI, the results are also conflicting, with two studies showing no association [86,97] and two studies showing an association [48,98] with cognitive disorders.

Delirium is a common cognitive negative outcome in hospitalized older people associated with drugs with anticholinergic activity. Identifying risk factors for delirium, specifically modifiable ones, is important for its prevention [5]. Although no conclusive theory exists, the most accepted hypothesis about the pathogenesis of delirium is based on a diffuse imbalance in cerebral neurotransmission including ACh as well as serotonin, noradrenaline, dopamine, and gamma-aminobutyric acid (GABA) [1,5,19], which may support the association between drugs with anticholinergic activity and delirium. Association between delirium and anticholinergic burden was studied for ARS, DBI, CrAS, ADS and ACB (Table 2). However, authors failed to confirm an association between ADS and ACB scores and this negative outcome.

Different confounders may influence the association of drugs with anticholinergic activity and cognitive outcomes. It is important to consider the possibility that the clinical condition can cause the outcome and not the drug with anticholinergic activity used, such as in Parkinson's disease [15,19]. Ignoring this can lead to reverse-causation bias, which should be solved using large longitudinal studies [19]. Additionally, drugs with anticholinergic activity can bind to other non-muscarinic receptors, which could modulate anticholinergic activity [19]. Finally, other neurotransmitters are involved in attention and memory processes [4], which indicates that central adverse effects can appear from non-muscarinic mechanisms [17].

Differences in the methods used to measure cognitive function impairment can also influence the results. Kashyap et al. found considerable variability in the incidence of cognitive decline that ranged from 8 to 86 % depending on the test used [83]. The different definitions and criteria used to measure cognitive impairment may result in either over- or underdiagnosis [15]. Statistical methods may also produce misleading conclusions. Lavrador et al. demonstrated that the associations found using null hypothesis tests were negligible when their effect size measures were taken into consideration [63].

4.3.2. *Functional and physical outcomes*

Several studies have been developed to evaluate the relationship between anticholinergic burden and physical and functional negative outcomes in older people. Apparently, these outcomes are the result of a combination of anticholinergic central and peripheral effects, namely, mental confusion or excitement, dyskinesia, lethargy, insomnia, lightheadedness, and headache or dry mouth, nausea, difficulty with visual accommodation, and cycloplegia [5]. The majority of the studies have cross-sectional and longitudinal designs, and their results are discrepant (Table 3) [19].

Koyama et al. [94] and Pasina et al. [85] found an association between ACB scores and functional impairment measured with different scales (*i.e.*, the Instrumental Activities of Daily Living (IADL) and the Barthel Index, respectively). The results for ADS were inconsistent even when a common outcome measure such as the Barthel Index was used [81,82]

All the studies evaluating the ARS demonstrated an association with impaired physical and functional performance. [103,82,85,86,88,102].

Also, the association between the DBI and functional outcomes has been evaluated in several studies, with all of them showing positive associations. Hilmer et al., when originally developing the DBI, found a

Table 3
Association between Anticholinergic burden scales and indexes and functional and physical outcomes.

Anticholinergic burden scale/tool	Study	Setting and population	Outcomes studied	Association
Clinician-rated Anticholinergic Scores	Han, 2008 [43]	Prospective cohort Community-dwelling	Executive function (Instrumental Activities of daily living)	+
	Agar, 2009 [12]	RCT Palliative care	Quality of life (McGill's Quality of life index)	+
			Functional outcome (Karnofsky performance scale)	+
	Yeh, 2013 [76]	Prospective cohort Veteran dementia care home	Functional outcome (Barthel Index)	–
Anticholinergic Drug Scale	Agar, 2009 [12]	Longitudinal Palliative care	Functional outcome *(Karnofsky performance scale)*	+
	Kersten, 2013 [81]	Cross-sectional Nursing-home residents	Functional outcome (Barthel Index)	–
Anticholinergic Risk Scale	Lampela, 2013 [82]	Cross-sectional Community-dwelling	Functional outcome (Barthel Index and Instrumental activities of daily living)	+
	Lowry, 2011 [102]	Cohort prospective Hospital	Functional outcome (Barthel Index)	+
	Koshoedo, 2012 [103]	Cohort Rehabilitation unit	Functional outcome (Barthel Index)	+
	Lampela, 2013 [82]	Cross-sectional Community-dwelling	Functional outcome (Barthel Index)	+
	Pasina, 2013 [85]	Cross-sectional prospective Hospital	Functional outcome (Barthel Index)	+
	Bostock, 2013 [86]	Observational prospective Hospital	Functional outcome (Barthel Index)	+
	Landi, 2014 [88]	Cohort Nursing home residents	Functional outcome (Barthel Index)	+
Anticholinergic Cognitive Burden Scale	Pasina, 2013 [85]	Cross-sectional prospective Hospital	Functional outcome (Barthel Index)	+
	Koyama, 2014 [94]	Prospective Community-dwelling	Functional outcome (Instrumental activities of daily living)	+
Drug Burden Index	Hilmer, 2007 [48]	Cross-sectional Community-dwelling	Physical Performance *(Health ABC performance score)*	+
	Cao, 2008 [98]	Cross-sectional Community-dwelling	Activities of daily living (self-reported), gait speed, balance, mobility, grip strength	+
	Gnjidic, 2009 [104]	Cross-sectional Community-dwelling	Walking speed, balance, grip strength and instrumental activities of daily living	+
	Gnjidic, 2012 [105]	Cross-sectional Community-dwelling	Walking speed, *Time Up and Go test*, instrumental activities of daily living, Barthel Index	+
	Gnjidic, 2012 [106]	Cross-sectional Nursing home residents	Physical Performance *(Short Physical Performance Battery)*	+
	Bostock, 2013 [86]	Observational prospective Hospital	Functional outcome (Barthel Index)	+
	Lowry, 2012 [107]	Cohort prospective Hospital	Functional outcome (Barthel Index)	+
Chew's list	Lampela, 2013 [82]	Cross-sectional Community-dwelling	Functional outcome (Barthel Index and Instrumental activities of daily living)	+

relationship between higher anticholinergic exposure and impaired physical function after adjustment for potential confounders, which was not found when nonmuscarinic and nonsedative drugs were analyzed as a group [48]. A second study by Hilmer et al. that aimed to evaluate the DBI performance confirmed these findings with an estimate of functional decline in community-dwelling older people of approximately 5 years [108].

The association of anticholinergic burden scales and peripheral anticholinergic adverse effects, particularly dry mouth, dry eyes, and constipation, is insufficiently studied. Rudolph et al. [49] demonstrated that ARS scores had a positive association with dry mouth, dry eyes and constipation. The ADS presented a significant association with dry mouth in 2 studies [12,81] but not with constipation [12]. Lavrador et al. [63] demonstrated that the ARS performed better than the ACB, ADS and DBI in predicting these peripheral negative outcomes, although the effect size was weak.

4.3.3. Falls

Falls are also associated with the use of drugs with anticholinergic activity, probably caused by a combination of other anticholinergic adverse effects including weakness, mental confusion, lightheadedness, and blurred vision [5]. However, evidence regarding the association of falls with anticholinergic burden is conflicting. Potential confounders such as cognitive impairment, behavioral disorders, incontinence, polypharmacy, and poor physical performance are often associated with anticholinergic prescriptions, and they could also explain an increased risk of falls (Table 4) [5].

Fraser et al. [109] conducted a study that evaluated fall and fracture risk associated with drugs with scores of 2 or 3 with the ARS and drugs with a score of 3 with the ABC, demonstrating an association in baseline and after 5 and 10 years. However, after adjustment for potential confounders, this association was no longer significant, which demonstrated that drugs with anticholinergic activity were not independently associated with risk of falls and fractures [109]. In a retrospective study, Best et al. [96] also examined the association between DBI scores and the risk of hospital admission for falls, but no association was found.

In a large population-based study with 19.4 years of follow-up, Tan et al. [110] demonstrated that baseline ACB scores were associated with a four-fold increased risk of hospitalization with falls, hospitalization with any fracture or hospitalization for hip fracture. Positive associations were also found for Aizenberg's scale, ARS, DBI and DBI-WHO in studies with distinct clinical settings (Table 4).

Table 4
Association between Anticholinergic burden scales and indexes and falls.

Anticholinergic burden scale/tool	Study	Setting and population	Outcomes studied	Association
Aizenberg's Anticholinergic Burden Scale	Aizenberg, 2002 [44]	Prospective Hospital	Falls	+
Anticholinergic Burden Classification	Fraser, 2014 [109]	Cohort prospective Community	Falls	–
Anticholinergic Risk Scale	Rudolph, 2008 [49]	Cohort retrospective Hospital	Falls	+
	Rudolph, 2008 [49]	Cohort prospective Primary care	Falls	+
	Fraser, 2014 [109]	Cohort prospective Community	Falls	–
	Landi, 2014 [88]	Cohort Nursing home residents	Falls	+
Anticholinergic Cognitive Burden Scale	Tan, 2020 [110]	Longitudinal cohort Community	Falls	+
Drug Burden Index	Wilson, 2011 [111]	Retrospective Nursing home residents	Falls	+
	Best, 2013 [96]	Retrospective Hospital	Falls	–
	Dauphinot, 2014 [55]	Longitudinal Hospital	Falls	+
Drug Burden Index –WHO	Dauphinot, 2014 [55]	Longitudinal Hospital	Falls	+

4.3.4. Hospitalization and mortality

The impact of anticholinergic burden on hospitalization and mortality has also been the subject of several studies. However, the findings are conflicting (Table 5).

In a large study with 537,387 older individuals in New Zealand, Nishtala et al. [118] found that higher DBI scores were associated with fall-related hospitalizations, a greater number of general practitioner visits, and a higher mortality risk. Salahudeen et al. [72] also performed a population-based study to investigate the association of 9 anticholinergic burden scales with hospital admissions, hospitalizations for falls, hospital length of stay and visits to general practitioners and demonstrated a significant association with all scales, and the DBI was the tool with the strongest predictive ability. In a cohort study of 16,603 patients with Alzheimer's disease, Gnjidic et al. [119] evaluated the impact of the DBI on hospitalization and mortality in older people with and without Alzheimer's disease and found an association with both hospitalization and mortality in older people with and without the disease [119]. Lönnroos et al. [116] conducted a 1-year follow-up prospective observational study in a population of community-dwelling older patients and reported that higher DBI scores were associated with a greater hospitalization rate and number of hospital days per person-year. Conversely, 4 studies found no significant association between increasing DBI scores and mortality (Table 5). Lowry et al. [102] found that ARS scores predicted in-hospital mortality in patients with hyponatremia. Fox et al. [2] demonstrated that the two-year mortality was greater in patients with higher ACB scores among the 13,004 patients followed. Kalish et al. [113] investigated the association between the use of drugs included in the ARS and ADS and the risk of hospitalization for confusion or dementia among 36,015 community older patients and found a significantly greater risk when individuals were taking two or more of these drugs.

Table 5
Association between Anticholinergic burden scales and indexes and hospitalization and mortality.

Anticholinergic burden scale/tool	Study	Setting and population	Outcomes studied	Association
Anticholinergic Drug Scale	Mangoni, 2013 [112]	Cross-sectional Hospital	Mortality	–
	Kalish, 2014 [113]	Retrospective Community-dwelling	Hospitalization	+
	Salahudeen, 2015 [72]	Pharmacoepidemiological study	Hospitalization	+
	Lowry, 2011 [102]	Prospective cohort Hospital	Mortality	+
	Kumpula, 2011 [114]	Prospective cohort Hospital and long-term care	Mortality	–
Anticholinergic Risk Scale	Mangoni, 2013 [112]	Cross-sectional Hospital	Mortality	+
	Kalish, 2014 [113]	Retrospective Community-dwelling	Hospitalization	+
	Salahudeen, 2015 [72]	Pharmacoepidemiological study	Hospitalization	+
	Fox, 2011 [2]	Longitudinal cohort Community-dwelling and institutionalized participants	Mortality	+
Anticholinergic Cognitive Burden Scale	Mangoni, 2013 [112]	Cross-sectional Hospital	Mortality	–
	Kidd, 2014 [115]	Retrospective Hospital	Mortality	–
	Salahudeen, 2015 [72]	Pharmacoepidemiological study	Hospitalization	+
	Lönnroos, 2012 [116]	Observational prospective cohort Community-dwelling	Hospitalization	+
	Wilson, 2012 [117]	Retrospective Nursing home residents	Mortality	–
	Lowry, 2012 [107]	Prospective cohort Hospital	Mortality	–
Drug Burden Index	Mangoni, 2013 [112]	Cross-sectional Hospital	Mortality	–
	Nishtala, 2014 [118]	Cross-sectional Community/Database	Hospitalization Mortality	+ +
	Gnjidic, 2014 [119]	Retrospective cohort Community/Database	Hospitalization Mortality	+ +
	Dauphinot, 2014 [55]	Longitudinal Hospital	Mortality	–
	Salahudeen, 2015 [72]	Pharmacoepidemiological study	Hospitalization	+

Mangoni et al. [112] also studied the capacity of the ARS, ADS, ACB and DBI to predict all-cause mortality in a population of older patients hospitalized for hip fractures and concluded that only higher ARS scores independently predicted 3-month mortality. However, Kumpula et al. [114] could not find an association between ARS scores and 1-year all-cause mortality in a cohort of 1004 long-term care residents.

4.4. Increasing the predictive ability of anticholinergic burden tools

In general, the literature suggests that anticholinergic burden measured with anticholinergic burden scales and tools is associated with negative clinical outcomes, such as cognitive and functional impairment, falls, hospitalization, and mortality. However, this evidence is still inconclusive, and clinicians cannot identify which scale or index better predicts one outcome or a group of outcomes. The heterogeneity identified among studies designing or assessing the performance of anticholinergic burden tools may be a reason for this weak and conflicting evidence.

The methods used to create the anticholinergic burden tools are very different, and different designs, populations, care settings, and tests to assess the outcomes were used [13]. Scales were applied to outpatients, inpatients, community dwellers, nursing home residents and databases [41]. Patients were heterogeneous in age, conditions, functional status, and frailty.

A universally accepted definition of drugs with anticholinergic activity is missing. Apart from drugs with muscarinic blockage as their main activity, a global list of drugs with demonstrated binding to muscarinic receptors is also missing. Thus, applying the tools in different scenarios from those in which they were developed can cause some inaccuracies [73].

When Mayer et al. [13] concluded that the predictive power of anticholinergic burden tools for determining clinical outcomes was modest, they suggested that not only drug doses but also other factors that modulate anticholinergic effects, such as patient characteristics, should be considered in the calculation of anticholinergic burden. Current anticholinergic burden tools work under the principle that if two different patients have the same anticholinergic burden according to one particular scale, they have the same risk of developing anticholinergic adverse effects. However, personal characteristics influence patients' susceptibility to developing anticholinergic effects. Therefore, to enhance the predictive yield of the scales, patient-related data should be considered in the calculations. A first step to personalize the scales could be considering pharmacokinetic parameters of drug metabolism and clearance in their calculations [17].

Available anticholinergic burden tools tend to simplify pharmacological mechanisms and, consequently, estimation of adverse effects might be inaccurate. Increased knowledge of the differential binding affinity of drugs with anticholinergic activity to specific muscarinic receptor subtypes could help to better predict potential anticholinergic adverse effects. This can be done with imaging techniques [120,121], but the high costs of these procedures prevent their use in clinical practice [34]. The selective binding to muscarinic receptor subtypes could point to different scores for each drug according to the adverse effect to predict, or simply, to different tools for the different adverse effects.

Network-based systems pharmacology models are suggested as possible approaches to be effective alternatives to better understand anticholinergic-type drug-induced adverse effects [34]. Systems pharmacology applies both experiments and computation to develop a deeper understanding of a drug's action ranging from the molecular and cellular levels to the tissue and organism levels, providing a mechanistic understanding of both therapeutic and adverse effects of drugs [122]. These studies help to identify new drug targets and predict adverse events, improving the safety and efficacy of drugs [122,123]. For instance, Salahudeen et al. [56] obtained positive results in a study that examined the effect of a nonlinear model framework including patient characteristics and considering binding to receptors to predict anticholinergic adverse effects in a population.

Finally, this narrative review has some limitations. As any narrative we made a comprehensive literature search, but no systematic search strategies were used. This means that we could present a good picture of the state of the art, but no systematic synthesis was intended. Additionally, although the review recommends that use of drugs that possess anticholinergic effects should be reduced in frail populations (*e.g.*, elderly), we have not aimed identifying alternative treatments to create a deprescribing guideline.

In summary, a great number of anticholinergic burden instruments are available in literature. However, none of them could be universally used (geographical limitation), many of them do not take into account the dose of the drug (potency limitation), all of them consider linear models for the cumulative effects (cumulative limitation), almost all ignore the pharmacological characteristics of the different muscarinic receptors (pharmacodynamic limitation), ignore the distribution of these receptors across the human body (pharmacokinetic limitation), and ignore frailty and susceptibility characteristics of patients (individual limitation).

To increase the prediction ability of a future anticholinergic burden tool, it should include all the drugs available in any country, take into account patient susceptibility considering personalized information (*i.e.*, pharmacokinetics and pharmacogenomics characteristics), differentiate the prediction estimates for the different anticholinergic adverse effects, and be amenable to inclusion in computerized clinical decision support systems. Collaboration between mechanistic pharmacology and clinical pharmacology researchers could create reliable instruments to guide clinicians to increase patient safety by reducing the negative outcomes caused by anticholinergic adverse effects.

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