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RESEARCH ARTICLE

Size of the associations between anticholinergic burden tool scores and adverse outcomes in older patients

Marta Lavrador[1,2] · Ana C. Cabral[1] · Isabel V. Figueiredo[1,2] · Manuel T. Veríssimo[2,3] · M. Margarida Castel-Branco[1,2] · Fernando Fernandez-Llimos[4]

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Abstract

Background Several anticholinergic scales and equations to evaluate the anticholinergic burden have been previously created. Association of these instruments with the anticholinergic outcomes are usually estimated by means of hypothesis contrast tests, which ignore the size of the association effect. *Objective* To evaluate the effect size of the associations between the scores on cumulative anticholinergic burden instruments with peripheral or central anticholinergic adverse outcomes in older patients. *Setting* Internal medicine ward of a Tertiary University Hospital. *Methods* A case–control study was conducted in patients over 65 years who were admitted to two internal medicine wards of a Portuguese university hospital. The Anticholinergic Drug Scale, Anticholinergic Risk Scale, Anticholinergic Cognitive Burden scale and Drug Burden Index were used to calculate the patients' anticholinergic burden. Peripheral (dry mouth—swab technique; dry eye—Schirmer test) and central (falls and cognitive impairment—Mini-Mental State Examination) anticholinergic adverse outcomes were investigated. The Barthel Index was used to assess overall physical functionality. The Mann–Whitney test was used to evaluate probabilistic differences in the anticholinergic scores between case and control individuals. To establish the effect size of the associations, the area under the curve of the receiver operating characteristics curve was calculated. *Main outcome measure* Anticholinergic adverse effects. *Results* A total of 250 patients (mean age 81.67 years, standard deviation 7.768; 50% females) were included. In total, 148 patients (59.2%) presented with dry mouth, 85 (34%) with dry eye, 141 (56.4%) with impaired functionality, 44 (17.6%) with a history of falls and 219 (87.6%) with cognitive impairment. Significant differences ($p < 0.05$) were obtained for the majority of the associations between Anticholinergic Drug Scale, Anticholinergic Risk Scale, Anticholinergic Cognitive Burden and Drug Burden Index and adverse effects. Conversely, the effect sizes of these associations ranged from "fail" (area under the curve 0.5 to 0.6) to "fair" (area under the curve 0.7 to 0.8). *Conclusion* Although significant differences in the scores of anticholinergic burden instruments and adverse outcomes may exist, the effect sizes of these associations ranged from 'fail' to 'fair', which limits their utility in preventing anticholinergic adverse outcomes with medication review interventions.

Keywords Aged · Cholinergic antagonists · Reproducibility of results · Risk assessment · ROC curve

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✉ Fernando Fernandez-Llimos
fllimos@ff.up.pt

[1] Pharmacology and Pharmaceutical Care Laboratory, Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal

[2] Coimbra Institute for Clinical and Biomedical Research (iCBR), Coimbra, Portugal

[3] Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[4] Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal

Impacts on practice

- The strength of the association between different anticholinergic adverse events and anticholinergic burden tools varies among tools and outcomes.
- The weak association between anticholinergic burden tools and adverse outcomes limit their utility as explicit criteria in medication review services.
- To correctly estimate risk factor associations, the use of effect size measures to evaluate the association between risk predictive tools and adverse outcomes should be encouraged.

Introduction

The use of medicines with anticholinergic effects among older people is highly prevalent despite the growing recognition about the risks inherent in their use [1]. The literature shows that 20–50% of older people are routinely exposed to medicines with potential anticholinergic activity and reports that one-third to more than one-half of the medicines commonly prescribed for older people have potential anticholinergic activity [2].

The cumulative effect of using multiple medicines with anticholinergic properties, known as anticholinergic burden, is associated with important adverse effects: central effects (cognitive impairment, dizziness, sedation, confusion or delirium) and peripheral effects (dry mouth, dry eyes, constipation, urinary retention or increased heart rate) [3]. Additionally, drugs with anticholinergic effects are associated with adverse outcomes such as falls, functional impairment, and higher hospitalisation and mortality rates [3–6].

Several methods have been developed to determine the anticholinergic activity of drugs based on serum anticholinergic activity (SAA) or in vitro affinity to muscarinic receptors. However, to translate these pharmacological concept into clinical practice, expert-based lists of drugs with anticholinergic activity, known as cumulative anticholinergic burden instruments, were created [7, 8].

Anticholinergic burden instruments are intended to be tools used in clinical practice for the anticipation of anticholinergic adverse events in older people [3, 9]. A recent systematic review identified eighteen different scales to quantify anticholinergic burden [10]. This review has demonstrated that the most frequently used instruments validated with adverse outcomes were the Anticholinergic Cognitive Burden Scale (ACB), Anticholinergic Risk Scale (ARS), Anticholinergic Drug Scale (ADS) and Drug Burden Index (DBI). The goals intended with these instruments were compiled in supplementary material - appendix 1.

However, the association between these tools and anticholinergic adverse outcomes varies and has not been conclusively established, since there is no standardized or consistent classification to measure anticholinergic exposure [2, 4, 6, 7]. Additionally, authors tend to present the results of these association analyses in terms of statistical significance, dichotomizing the *p* values as significant or non-significant, instead of measuring the real magnitude of the effects through effect sizes measures [11]. Therefore, it remains unclear what scale better reflects the anticholinergic burden and, consequently, which one better predicts important anticholinergic outcomes.

Aim of the study

Our aim was to evaluate the effect size of the association between instruments to measure the cumulative anticholinergic burden with peripheral or central anticholinergic adverse outcomes in older patients.

Ethics approval

This study was approved by Ethics Committee of University of Coimbra Teaching Hospital (Approval Number CHUC-006-18).

Methods

Population

A case–control study was conducted, between May 2018 and April 2019, in patients over 65 years admitted to two internal medicine wards of a Portuguese university hospital. Patients taking at least one medicine at the time of admission were included. The exclusion criteria comprised patients who were unable to adequately answer to the questionnaires due to physical or mental disability, patients with diagnosed dementia, and patients who were taking acetylcholinesterase inhibitors (e.g., donepezil, galantamine, rivastigmine). Informed consent was obtained from all individual participants included in the study.

Sociodemographic data were collected. Hospital medical records (HMR) were appraised to collect clinical information related to admission, including both admission diagnoses and previous diagnosis, and medicines used at the time of admission. To correctly establish the patients' medication profiles, primary care electronic health records (EHR) from

the preceding 6 months were consulted. This period was considered based on a previous study that demonstrated that the most efficient medication data retrieval process should consider a 6-months retrospective analysis of the EHR [12]. Medication profiles, including prescription and non-prescription medicines, were complemented with an interview with the patient or the caregiver within 48 h after admission. The information from these three sources (HMR, EHR and patient/caregiver) was gathered, and medicines were included in the best possible medication history (BPMH) at admission when a) a prescription medicine existed in one of the mentioned sources and the use was confirmed by the patient/caregiver; and b) the use of a non-prescription medicine was reported by the patient/caregiver. Combination medications were treated as multiple individual medications taken at a single time point. Drugs were classified according to the Anatomical Therapeutic Chemical Code (ATC). The international non-proprietary names, dosages, pharmaceutical forms and regimes of each medicine were compiled.

Instruments

Exposure to anticholinergic drugs was calculated by the summation of the drug scores for each of the three anticholinergic risk scales (the Anticholinergic Risk Scale (ARS), the Anticholinergic Drug Scale (ADS) and the Anticholinergic Cognitive Burden Scale (ACB)) and one equation (the anticholinergic component of the Drug Burden Index (DBI)) applied to the long-term medicines used by the population of older adults under study.

Anticholinergic Risk Scale (ARS): The ARS includes 49 drugs. The drugs listed in the ARS are scored on a 0 to 3 scale, with 0 indicating no known anticholinergic activity and 3 indicating high anticholinergic affinity considering the muscarinic receptor dissociation constant, the rates of anticholinergic effects versus placebo in experimental studies, and a review of the literature on anticholinergic central and peripheral adverse effects [13].

Anticholinergic Drug Scale (ADS): The ADS includes 115 drugs and has four score levels for each included drug: drugs with no known anticholinergic properties—score 0; drugs with potentially anticholinergic activity as evidenced by receptor binding studies—score 1; drugs with anticholinergic adverse events, usually at excessive doses—score 2; and drugs with marked anticholinergic properties—score 3 [14].

Anticholinergic Cognitive Burden Scale (ACB): The ACB is a scale based on a systematic review that assessed the anticholinergic adverse events on cognition for both prescription and non-prescription medicines. An expert panel established the following scoring system: "evidence from in vitro data that the medication has antagonist activity at muscarinic receptors—score 1"; "evidence from the literature, prescriber's information, or expert opinion of clinical anticholinergic effect—score 2" and "evidence from the literature, prescriber's information, or expert opinion of the medication causing delirium—score 3". The list includes 99 medications with anticholinergic activity that were associated with negative cognitive effects [15]. For each patient, drugs were scored according to the three scales.

Drug Burden Index (DBI): The DBI calculates exposure to both anticholinergic and sedative medications based on the principles of dose–response and maximal effect, according to the following equation:

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

where B_{AC} indicates de anticholinergic burden and B_S the sedative burden. This pharmacological model assumes that the anticholinergic and sedative burdens of individual drugs are additive and linear.

In the present study, only the anticholinergic component of DBI (B_{AC}) was considered. The DBI for each drug with anticholinergic effect was calculated using the following equation:

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

where D is the daily dose taken by the subject and δ is the minimum recommended daily dose, as an estimate of the dose required to achieve 50% of the maximum anticholinergic effect (DR_{50}) [16]. The minimum recommended daily dose was defined according to the British National Formulary (BNF) considering the minimum daily dose used for the most common indications. The minimum recommended daily dose for drugs that were used by the study population but not included in the BNF—(i.e., cyclobenzaprine, estazolam and clorazepate) was calculated using the minimum recommended daily dose approved by each drugs' official summary of product characteristics approved in Portugal. The original list of drugs reported in the first DBI publication was considered to calculate the DBI [17]. Only the drugs with anticholinergic effects were considered [18]. Medications with both anticholinergic and sedative effects were classified as anticholinergic, as indicated in previous studies [16, 17, 19].

Outcome measures

Peripheral (i.e., dry mouth and dry eye) and central (i.e., falls and cognitive impairment) anticholinergic outcomes were assessed. Dry mouth: Mouth dryness was measured by a swab technique [20]. This method consists of placing two pre-weighted dental cotton rolls at the patients' orifices of the ducts of the salivary glands. The increase in weight of the cotton rolls in a fixed time interval, transformed to either grams per minute or millilitres per minute, corresponds to

salivary flow. The rolls were weighed before and after the procedure using an electronic device sensitive to 0.01 g [21]. Salivary flow rates < 0.1 ml/min were considered dry mouth [22]. This swab test was performed consistently in relation to the time of collection. Also, patients were refrained from eating or drinking 1–2 h prior to the test session.

Dry eye: Eye dryness was assessed by performing the Schirmer test. This test measures the total tear secretion and is the sum of reflex and basal tear flow. The Schirmer test consists of placing a 35 mm × 5 mm dry sterile filter paper strip over the middle to lateral 1/3 of the lower eyelid. The patient is then instructed to close their eyes. The strip is removed after 5 min, and the amount of wetting is recorded in millimetres. A value below 10 mm was considered as dry eye [23].

Physical functionality: The Barthel Index was used to assess ability in basic activities of daily living. It encompasses 10 variables describing activities of daily living and mobility (i.e., feeding; bathing; grooming; dressing; bowel control; bladder control; toilet use; transfers from bed to chair and back; mobility on level surfaces; stairs) and yields scores of 0–100 [24]. A high score is associated with a higher level of independence or functionality. Patients can be divided into five degrees of dependence: total (scores: 0–24), severe (scores: 25–49), moderate (scores: 50–74), mild (scores: 75–90) and minimal impairment (scores 91–100) [25]. The Barthel Index was applied to each patient by a trained researcher within 48 h of hospital admission. Patients with Barthel Index ≤ 90 were considered to have functional decline.

Falls: During the interviews, the patients or their caregivers were asked about the occurrence of falls in the preceding 6 months. Additionally, the patients' hospital records and other electronic health records were consulted to access clinical data that could confirm the information provided.

Cognitive impairment: The Mini-Mental State Examination (MMSE) is a widely used cognitive screening test [26]. The MMSE was used to determine patients' cognitive function and was performed within 48 h of hospital admission. A score ≤ 26 was considered as cognitive impairment [27].

Data analysis

To characterize the study population, means with standard deviations (SD) or medians with interquartile ranges (IQR) were calculated for continuous data. For categorical variables, the absolute numbers and percentage proportions were used. The Shapiro–Wilk (SW) test was used to assess the normality of anticholinergic burden scale scores and DBI data.

The sample size was calculated using the OpenEpi (CDC; Atlanta, GA) sample size calculator for unmatched case–control studies (https://www.openepi.com/SampleSize/SSCC.htm) considering an alpha error of 0.05, a statistical power of 80%, a 1 ratio cases-to-controls, 80% versus 60% proportion of exposure in cases versus controls (least extreme odds ratio = 0.38). The minimum sample size calculation ranged from 168 with Fleiss methods to 188 with Fleiss with continuity correction.

To evaluate probabilistic differences in the anticholinergic scores between case and control individuals, the Mann–Whitney test was used, with a significance limit established at 0.05.

To establish the effect size of the association between the cumulative anticholinergic scores and the anticholinergic adverse outcomes, first the Cohen's d was computed using the Psychometrica calculator (https://www.psychometrica.de/effect_size.html) based on Fritz et al. formulas [28]. Cohen's d represents the magnitude of the effect with the following intervals recommend by Cohen [29]: 0–0.2 no effect, 0.2–0.5 small effect, 0.5–0.8 intermediate effect, and > 0.8 large effect. Additionally, the area under the curve (AUC) of the receiver operating characteristic (ROC) was calculated. ROC curves consist of plotting sensitivity versus 1-specificity. ROC curves were used to estimate the association between the continuous variable (i.e., score of each instrument) and the occurrence of each anticholinergic adverse outcome). AUC is an effective measure of accuracy to determine the inherent ability of a continuous scale to discriminate between individuals having or not having the anticholinergic outcome by combining measures of sensitivity and specificity. The AUC can be taken as the probability that a randomly chosen patient with an anticholinergic outcome is rated or ranked as more likely to have this outcome than a randomly chosen patient who does not have the outcome [30]. An AUC value of 1 represents a perfect association with the anticholinergic outcome, while a result of 0.5 corresponds to a worthless accuracy. AUC values between 0.90–1 are considered 'excellent'; 0.80–0.90 'good'; 0.70–0.80 'fair'; 0.60–0.70 'poor'; 0.50–0.60 'fail' [31].

To evaluate the potential effect of patients' clinical conditions as confounders in the association with anticholinergic adverse outcomes, multivariate analyses for the score of each anticholinergic burden tool were performed using age, gender and the presence of diabetes, autoimmune diseases, or other diseases with potential dehydration effects as covariates of the analysis [32].

A sensitivity analysis was performed through the creation of two composite variables: a) presenting more than 1 anticholinergic effect and b) presenting more than 2 anticholinergic effects. Sensitivity analyses were made by calculating the AUC of ROC curves of both composite variables.

Results

A total of 250 patients with a mean age of 81.67 years (SD = 7.8) and 50% of each gender were included. These patients were using 2556 drugs, with 2386 used as long-term drugs and 170 used as PRN drugs. The most prevalent long-term drugs belonged to cardiovascular (30.4%) and nervous (20.1%) system medications, according to ATC classification.

The ADS identified a total of 209 patients (83.6%) with at least one drug with anticholinergic effects; the ARS identified 96 patients (38.4%), the ACB identified 195 patients (78%), and the DBI identified 170 patients (68%) with one of these drugs. All anticholinergic burden scales and DBI scores were not normally distributed with SW p values < 0.001, which was confirmed by visual inspection of the Q–Q plot. The median scores obtained for the scales were 2.0 (IQR = 2; range 0–9) for the ADS, 0.0 (IQR = 1; range 0–7) for the ARS, and 2.0 (IQR = 2; range 0–11) for the ACB, and the median score of the DBI was 0.50 (IQR = 1.214; range 0.0–2.981).

The swab test (SW $p < 0.001$) yielded a median of 0.08 (SD = 0.07) with 148 (59.2%) patients presenting with dry mouth. The median score of the Barthel Index (SW $p < 0.001$) was 90 (IQR 60), classifying 141 (56.4%) individuals as having impaired physical functionality. The median MMSE was 19 (IQR 11), identifying 219 (87.6%) patients with cognitive impairment. Additionally, a history of falls was recorded in 44 individuals (17.6%), and 85 (34%) patients presented with dry eye.

When performing typical non-parametric null hypothesis significance tests (i.e. Mann–Whitney) to evaluate the differences in the scores between individuals who did and did not present with anticholinergic effects, significant differences were obtained for the majority of the anticholinergic adverse outcomes. Exceptions to this were found only in the association between falls with the ADS, ACB and DBI, and for cognitive impairment with the ADS and ACB (Table 1). However, when translating these U values into Cohen's d effect size measures, large effect sizes (d > 0.8)

Table 1 Differences between the distributions of anticholinergic burden scale scores and occurrence of anticholinergic adverse outcomes

Outcome	Scale	Median	IQR	Median	IQR	p value*	Cohen's d
Dry mouth		Yes (n = 148)		No (n = 102)			
	ADS	2	1–3.75	1.5	0–2	< 0.001	0.498
	ARS	1	0–2	0	0–0	< 0.001	0.876
	ACB	2	1–4	1	0–2	< 0.001	0.728
	DBI	0.750	0.400–1.539	0.125	0–0.667	< 0.001	0.803
Dry eye		Yes (n = 85)		No (n = 165)			
	ADS	2	1–4	2	1–3	0.020	0.291
	ARS	1	0–2	0	0–0	< 0.001	0.819
	ACB	3	1–5	1	0–2	< 0.001	0.665
	DBI	0.964	0.450–1.640	0.500	0–0.982	< 0.001	0.562
Impaired functionality		Yes (n = 141)		No (n = 109)			
	ADS	2	1–3	1	0.5–2.5	0.002	0.389
	ARS	1	0–2	0	0–0	< 0.001	0.629
	ACB	2	1–4	1	0–2	0.002	0.390
	DBI	0.714	0.400–1.467	0.400	0–0.690	< 0.001	0.616
Falls		Yes (n = 44)		No (n = 206)			
	ADS	2	1–3	2	1–3	0.567	0.071
	ARS	1	0–2	0	0–1	0.029	0.242
	ACB	1.5	1–3.75	2	1–3	0.617	0.062
	DBI	0.690	0.100–1.304	0.500	0–1.117	0.142	0.183
Cognitive impairment		Yes (n = 219)		No (n = 31)			
	ADS	2	1–3	1	0–3	0.121	0.193
	ARS	0	0–1	0	0–0	0.018	0.263
	ACB	2	1–3	1	0–3	0.092	0.210
	DBI	0.571	0–1.250	0.400	0–0.750	0.030	0.272

*Mann–Whitney test

ADS Anticholinergic Drug Scale, *ARS* Anticholinergic Risk Scale, *ACB* Anticholinergic Cognitive Burden scale, *DBI* Drug Burden Index

were obtained only for dry mouth in ARS and DBI, and for dry eye in ARS (Table 1).

Conversely, when the association of the instruments with the anticholinergic adverse outcomes was assessed by using the AUC as the effect size measure, the results ranged from'fail' (i.e., from 0.5 to 0.6) to 'fair' (i.e., 0.7 to 0.8). The lowest AUC value (0.524; 95% CI 0.428–0.619) was found for the association between falls and the ACB scale, while the highest was for the association of dry mouth (0.736; 95% CI 0.675–0.797) with the ARS scale (Table 2). The ROC curves for each of the analysed outcomes and the instruments are presented in supplementary material - appendix 2.

In the multivariate analyses to identify the potential influence of patients' characteristics and comorbidities as confounders on the association between anticholinergic burden and the outcomes under analysis, significant associations were found for the instruments for all the outcomes (except for falls), but only age presented association with dry mouth and cognitive impairment but not with dry eye. As expected, impaired daily living, measured by the Barthel index, also presented association with 'other conditions' (supplementary material – appendix 3).

Sensitivity analyses demonstrated no improvement of the two composite variables (i.e. more than 1 and more than 2 anticholinergic effects) compared with the highest associated outcome (i.e., dry mouth) (supplementary material - appendix 4).

Table 2 Effect sizes (measured as areas under curve) of the association between anticholinergic burden scales scores and occurrence of anticholinergic adverse outcomes

	AUC	95%CI	*p* value
Dry mouth			
ADS	0.642	0.574–0.711	< 0.001
ARS	0.736	0.675–0.797	< 0.001
ACB	0.701	0.638–0.765	< 0.001
DBI	0.719	0.656–0.782	< 0.001
Dry eye			
ADS	0.588	0.511–0.665	0.023
ARS	0.731	0.663–0.800	< 0.001
ACB	0.693	0.621–0.764	< 0.001
DBI	0.665	0.593–0.737	< 0.001
Impaired functionality			
ADS	0.611	0.541–0.682	0.003
ARS	0.675	0.609–0.741	< 0.001
ACB	0.612	0.542–0.681	0.002
DBI	0.672	0.605–0.739	< 0.001
Falls			
ADS	0.527	0.434–0.620	0.575
ARS	0.591	0.496–0.687	0.058
ACB	0.524	0.428–0.619	0.624
DBI	0.569	0.477–0.662	0.150
Cognitive impairment			
ADS	0.584	0.461–0.707	0.129
ARS	0.614	0.513–0.716	0.039
ACB	0.592	0.482–0.702	0.099
DBI	0.618	0.516–0.721	0.033

ADS Anticholinergic Drug Scale, *ARS* Anticholinergic Risk Scale, *ACB* Anticholinergic Cognitive Burden scale, *DBI* Drug Burden Index (DBI), *AUC* Area under curve (AUC), *CI* Confidence Interval

Discussion

In a population of older people admitted to internal medicine wards, almost all the associations between anticholinergic scale scores and anticholinergic adverse outcomes were statistically significant according to probabilistic tests. However, the effect sizes measured by the AUC of ROC curves demonstrated that the associations ranged from 'fair' (maximum AUC = 0.736) to'fail' (minimum AUC = 0.524).

Many studies have reported the association between the anticholinergic burden measured by cumulative anticholinergic burden instruments and anticholinergic adverse outcomes. In fact, five systematic reviews compiled the evidence regarding these associations [4–6, 9, 10]. These systematic reviews have shown that the different scales present different association levels with patients' anticholinergic adverse outcomes. These discrepancies can be a result of the different methods and validation procedures used to create the anticholinergic burden instrument, and can be produced by inconsistencies in how drugs with anticholinergic effects were identified and scored. Salahudeen et al. underlined the subjective rating of anticholinergic activity, which is highly dependent on the knowledge of expert panels about anticholinergic adverse effects [4]. Additionally, the differences in the selection of the outcomes, the metrics used to assess them, and the heterogeneity of the settings where the outcomes were validated varied substantially. Particularly, the outcomes mainly reported include cognitive outcomes (i.e., cognitive impairment, confusion, dizziness, falls and delirium) and functional or physical outcomes (i.e., activities of daily living, physical performance, mouth dryness, eye dryness and constipation). Other outcomes of interest frequently reported include serum anticholinergic activity (SAA), hospitalisation, length of hospital stay and mortality.

Although 18 different cumulative anticholinergic burden instruments have been identified thus far, the most frequently validated tools to predict the occurrence of anticholinergic adverse outcomes are the ADS, ARS, ACB and DBI. A recent overview of systematic reviews demonstrated that all studies reporting outcomes related to falls and hospitalisation found an association with anticholinergic burden. This overview also describes that the majority of the studies that assessed mortality, delirium and physical function outcomes

reported an association with anticholinergic burden. However, although a majority of studies included in this overview reported an association with cognitive function, the number of participants was higher in the studies that found no association [10].

It is important to note that all the existing evidence about the association of the anticholinergic burden instruments and the anticholinergic adverse effects is based on measures of *p* values searching for significant associations. The use of this statistical approach is highly debated by the scientific community. The American Statistical Association (ASA) has recently published an issue including 43 articles about *p* values and statistical significance and other related topics such as null hypothesis statistical testing, sample size, and alternatives to *p* value [33]. Schreiber advocates that reporting only the *p* values and dichotomizing the *p* values as significant or non-significant is not enough to fully understand the results [34]. Alternatively, the reporting of effect size measures is being encouraged because it reveals the magnitude of the differences found and not just that the effect exists [11].

In our study, almost all the associations between the scales and the adverse outcomes showed statistical significance as measured when dichotomizing the *p* values. However, the AUCs of the ROC curves showed that none of the anticholinergic scales achieved 'good' or 'excellent' association with anticholinergic adverse outcomes, with the majority of the associations classified as 'fail' or 'poor'. The ARS presented slightly better effect size measures than the other three instruments analysed. Additionally, the ARS developers aimed to measure both central and peripheral anticholinergic effects of drugs [13]. In fact, the literature shows that the ARS is the most frequently used tool in care homes and hospital settings [10].

Regarding peripheral anticholinergic adverse effects, the association between the instruments and dry mouth was studied only in the ARS and ADS, with both tools showing a positive association [13, 35]. In our study, the ARS was the instrument with higher association with all the outcomes, followed by the DBI and ACB, with the ADS as the worst scale. The association with eye dryness has only been studied for the ARS [13], which also obtained the best results in our study.

A systematic review conducted by Villalba-Moreno et al. that assessed the use of anticholinergic scales in multimorbid patients also found that the high anticholinergic burden measured by these tools had a negative impact on functional status [6]. Wouters found that higher DBI values were consistently associated with impairment in functionality [36]. In our study, the effects of anticholinergic adverse outcomes on physical functionality, assessed by the Barthel Index, were more associated with ARS and DBI, which is consistent with the previous literature [10].

Cognitive impairment is probably one of the most perturbing anticholinergic adverse outcomes. Whalley et al. confirmed previous literature that associated the use of drugs with anticholinergic activity with cognitive impairment, but they also demonstrated that these patients did not progress to dementia. Thus, excluding patients with diagnose of dementia for our study should not influence on the association analyses [37]. In our study, DBI and ARS were the scales with higher association, with the ADS as the worst option. This poor ADS performance can be explained by the fact that this scale was created based on the effects of the drugs on serum anticholinergic activity, without focusing on their cognitive effects [14]. Although the ACB was specifically developed to identify the severity of anticholinergic negative effects on cognition [38], in our study this scale showed poor association with cognitive impairment. Literature shows conflicting results of the association of DBI with cognitive impairment, with two studies showing no association [39, 40] and one presenting a positive relation [16].

Falls presented the weakest association with anticholinergic burden tools. The null hypothesis tests showed non significance for ADS, ACB, and DBI. Effect sizes calculated by the AUCs of the ROC curves resulted in 0.527, 0.591, 0.524, and 0.569 for ADS, ARS, ACB and DBI, respectively, which represent an almost null association. A recently published study on a large database of the EPIC-Norfolk study demonstrated a small-to-intermediate association of hospitalization by falls during 19 years follow-up, with even weaker association in patients over 60 years. This study failed explaining this decreased association in aged population, and ignored the use of medicines during the follow-up period (including new drugs with anticholinergic effects) [41].

The anticholinergic burden scales analysed categorize drugs with anticholinergic effects based on their hypothetical anticholinergic power, compiling different drugs across the scales. The poorer performance of ADS may be a consequence of being designed by a consensus panel using the SAA [14] to classify drugs regardless their ability to cross the blood–brain barrier, which is crucial for central anticholinergics effects [35, 42]. On the other hand, ARS best performance, previously reported in literature [10], may result from the combination of the analysis of the dissociation constant for cholinergic receptors with the actual prevalence of adverse effects reported in Micromedex [13]. All these scales have as a common limitation the fact of ignoring the doses of the drugs used by the patients. Conversely, DBI adopts a different approach based on dose/response principle, but also uses a subjective list of drugs with anticholinergic effects. All the tools have discrepancies in the drugs included and the scores attributed to them. A clear example of these inconsistencies is the absence of drugs whose primary action is precisely their anticholinergic effect, such as ipratropium bromide, tiotropium bromide or biperiden.

Additionally, the scales do not have into account the duration of use of the drugs. In fact, for different drugs, the influence of duration of use and the onset of effects can be different. Also, individual characteristics may lead to a greater susceptibility to the effects of drugs (e.g., renal function, comorbidities, polypharmacy). All of these aspects can affect the predictive ability of the anticholinergic burden tools and, consequently, the use of these tools to help guiding prescribing practice should be careful. Our study did not aim creating a predictive model based on these instruments, but measuring the association with the anticholinergic outcomes under analysis. A predictive model should, not only discriminate patients at risk to develop the adverse event from those who will not, but also calibrate the risk estimates [43]. However, as an important implication into practice of our study, it is important to bear in mind that these tools are among the instruments recommended as explicit criteria to be used in medication review [44]. When designing a recommendation in a medication review service for aged patients, the use of drugs with anticholinergic activity, and subsequently the anticholinergic burden, is probably the only modifiable risk factor that clinicians can consider to avoid the occurrence of anticholinergic adverse events. In this context, the effect size of the bivariate association between the score of these tools and the anticholinergic adverse event represents the ability to prevent patients' negative outcomes.

Limitations

The present study has some limitations. The results we obtained are limited to the older people admitted to internal medicine wards; these individuals may have specific conditions and determinants that may influence the generalizability of our results. Furthermore, in-hospital medications were not included in this study. However, outcomes' assessment was completed before 48 h of admission, which means that the expected influence of anticholinergic effects of inhospital drugs is very limited. Additionally, the assessment of falls data was performed with self-reporting and confirmation with hospital or EHR records which may be inaccurate. The list of medicines considered in the DBI calculation was based on the original list considered by Hilmer et al., which does not include some drugs marketed in our country that may have anticholinergic effects. Further analysis is needed to discuss the influence of using different lists of medicines to calculate the DBI.

Conclusions

Our study demonstrated that, although statistically significant differences in the scores of anticholinergic burden instruments between individuals with and without anticholinergic adverse outcomes may exist, the effect sizes of these associations ranged from 'fail' to 'fair', which limits their utility as indicators for clinical pharmacy interventions to reduce anticholinergic adverse outcomes. Our findings also reinforce that articles should always provide both null hypothesis significant tests and effect size measures to correctly interpret risk factor associations.

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