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Concordance among anticholinergic burden scales

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Royalties		X		X		X		X		X		X		X	
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Abstract

Background—There is no gold standard to assess potential anticholinergic burden of medications.

Objectives—To evaluate concordance among five commonly used anticholinergic scales.

Design—Cross-sectional secondary analysis.

Setting—Pittsburgh, PA, and Memphis, TN.

Participants—3,055 community-dwelling older adults aged 70–79 with baseline medication data from the Health, Aging, and Body Composition study.

Measurements—Any use, weighted scores, and total standardized daily dosage were calculated using five anticholinergic measures (i.e., Anticholinergic Cognitive Burden [ACB] Scale, Anticholinergic Drug Scale [ADS], Anticholinergic Risk Scale [ARS], Drug Burden Index anticholinergic component [DBI-ACh], and Summated Anticholinergic Medications Scale [SAMS]). Concordance was evaluated with kappa statistics and Spearman rank correlations.

Results—Any anticholinergic use in rank order was 51% for the ACB, 43% for the ADS, 29% for the DBI-ACh, 23% for the ARS, and 16% for the SAMS. Kappa statistics for all pairwise use comparisons ranged from 0.33 to 0.68. Similarly, concordance as measured by weighted kappa statistics ranged from 0.54 to 0.70 among the three scales not incorporating dosage (ADS, ARS, and ACB). Spearman rank correlation between the DBI-ACh and SAMS was 0.50.

Conclusions—Only low to moderate concordance was found among the five anticholinergic scales. Future research is needed to examine how these differences in measurement impact their predictive validity with respect to clinically relevant outcomes, such as cognitive impairment.

Keywords

cholinergic antagonists; aged; drug utilization

INTRODUCTION

Despite increasing awareness of the negative outcomes associated with anticholinergic medications, use remains prevalent among community-dwelling older adults.^{1–4} Highly anticholinergic drugs are generally classified as potentially inappropriate, as any benefits are outweighed by the risk of adverse drug events.^{5,6} Of particular concern are central nervous system toxicities, including confusion and cognitive impairment.^{7–9}

The continued widespread use of this medication class in older adults may be explained by differences in identifying agents with anticholinergic properties. In the United States alone, at least five scales are commonly used. First introduced in 2002 and validated against serum

anticholinergic activity (SAA), the Anticholinergic Drug Scale (ADS) utilizes an ordinal scale to rank medications based on anticholinergic potential.¹⁰ In this scale, level 0 drugs have no known anticholinergic properties; level 1 may be potentially anticholinergic based on SAA; level 2 have anticholinergic adverse effects noted at excessive doses; and level 3 are characterized as markedly anticholinergic. Weights for each anticholinergic medication can be summated to calculate an overall ADS score.

Published in 2008, the Anticholinergic Risk Scale (ARS) and Anticholinergic Cognitive Burden Scale (ACB) also use an ordinal scale to rank medications.^{11,12} To create the ARS, the most commonly prescribed drugs at a single Veterans Affairs Medical Center were weighted by an expert panel based on their *in vitro* dissociation constant for the cholinergic receptor, where 1 indicates moderate, 2 strong, and 3 very strong dissociation.¹¹ Alternatively, the ACB was developed based on expert panel consensus and a comprehensive literature review of anticholinergic drugs associated with delirium, cognitive decline, and dementia. For the ACB, drugs ranked as 0 have no anticholinergic effects, those ranked 1 have possible anticholinergic effects based on SAA or *in vitro* affinity for muscarinic receptors, and those classified as 2 or 3 are medications with established and clinically-relevant cognitive effects.¹² As with the ADS, within the ARS and ACB individual medications may be summated across agents to provide an overall anticholinergic burden score.

The anticholinergic component of the Drug Burden Index (DBI-ACh) includes medications with anticholinergic adverse effects listed in two pharmacology sources.^{13,14} The DBI-ACh considers the impact of individual medications by dividing a person's daily dose of each anticholinergic drug by the composite sum of that daily dose added to the minimum effective daily dose approved by the Food and Drug Administration. Thus, all scores are on a logarithmic scale ranging from 0 to 1, and can be summated across agents to create an overall burden score.^{13,14} Also incorporating dosage, the Summated Anticholinergic Medications Scale (SAMS) is based on expert panel consensus for the 2012 Beers criteria of drugs with strong anticholinergic properties, as well as previously published work with central nervous system drugs.^{15,16} Unlike the DBI-ACh, the SAMS creates a linearly scaled measure whereby anticholinergic drug daily dose is divided by the minimum effective geriatric daily dose listed in a standard geriatric pharmacotherapy text.¹⁷

To our knowledge, no studies have compared all five scales with regard to consistently quantifying anticholinergic burden in community-dwelling older adults. Therefore, this study aimed to evaluate concordance among these five commonly used anticholinergic scales.

METHODS

Study Design, Setting, Source of Data, and Sample

This cross-sectional analysis utilized existing data from the baseline visit of the Health, Aging, and Body Composition (Health ABC) study. Specifically, Health ABC study investigators consented and enrolled 3,075 black and white men and women aged 70–79 years without mobility limitations residing in areas surrounding Pittsburgh, Pennsylvania,

and Memphis, Tennessee. The current study sample includes 3,055 participants with complete medication data at study entry. The Health ABC study was approved by the University of Pittsburgh and the University of Tennessee Memphis institutional review boards.

Data Collection and Management

A full description of data collection and management used for the Health ABC study is presented elsewhere.¹⁸ Briefly, at the initial clinic visit trained research assistants collected sociodemographic characteristics, various aspects of physical health, and functional status from enrollees. These assistants also reviewed with participants all prescription and nonprescription medications used during the preceding two weeks and transcribed, using the actual drug vials or containers, the drug name, strength, dosage form, and the amount and frequency of use reported. All medications were numerically coded using the Iowa Drug Information System (IDIS) and entered into a computerized database.¹⁹

Anticholinergic Medication Use Exposure Variables

We contacted the authors of the five scales to acquire the most recent list of anticholinergic medications; more recent updates were received for the ADS and ACB. Medications not found in the United States or those with an expected short duration (i.e., antibiotics) were excluded. Using IDIS codes, we created exposure variables for the five anticholinergic measures. Regarding the scales not incorporating dosage, the ADS had 122 drugs, the ACB had 94 drugs, and the ARS had 50 drugs considered to have at least some anticholinergic potential (i.e., weight = 1) (e-Appendix 1). Twenty-nine medications were common to all three scales. A total standardized anticholinergic score for each scale was calculated by summing the scores for individual agents taken daily. For purposes of analysis, we created a dichotomous variable for any anticholinergic use and a categorical variable for summated scores (0, 1–2, 3) based on the distribution of data and clinical relevance.

Between those scales incorporating dosage, the DBI-ACh contained 74 drugs and the SAMS contained 41 drugs, with 38 medications in common. For both measures, we calculated average daily dose for each regularly-scheduled anticholinergic medication. For the DBI-ACh, we divided this value by the lowest adult minimum effective dose per the scale developers (e-Appendix 2). To facilitate comparison with the SAMS, the DBI-ACh was not transformed to a logarithmic scale. For the SAMS, we employed the lowest geriatric minimum effective daily dose per a standard pharmacotherapy source, which was also used by a recently published study.^{16,17} For analysis of both measures, individual anticholinergic standardized daily doses were summated across medications to create an overall total standardized daily dose (TSDD) for each participant. We also created a dichotomous variable for any use of anticholinergic drugs for each measure.

Statistical Analyses

Appropriate summary statistics were used to characterize several demographics (i.e., race, gender, age, study site, education, and cohabitation status), health status characteristics (i.e., self-rated health status, total number of medications), and the five anticholinergic exposure measures. Pairwise agreement for any anticholinergic use among the five scales was

assessed using kappa statistics (κ) to quantify concordance. For scales not considering dosage which yield categorical scores (ADS, ARS, and ACB), pairwise agreement was assessed with weighted kappa statistics. For scales incorporating dosage which yield continuous scores (DBI-ACh and SAMS), Spearman rank correlation (r_s) was used to quantify agreement. All statistics were calculated using SAS® software (version 9.43; SAS Institute, Inc., Cary, NC).

RESULTS

As seen in Table 1, participants were predominantly white, female, living with another person, and in good health. Overall, subjects were relatively well-educated, with fewer than 25% having less than a high-school education.

The average number of medications was nearly 2, and the average age was 74 years. The prevalence of any anticholinergic use was highest with the ACB at 51%, followed by the ADS at 43%, the DBI-ACh at 29%, the ARS at 23%, and the SAMS at 16%. Table 2 shows the kappa statistics comparing all five published scales, which ranged from 0.33 to 0.68.

Table 3 illustrates the number of Health ABC participants distributed across score categories for the ACB, ADS, and ARS. Weighted kappa statistics among these scales were 0.70 for the ACB versus ADS, 0.54 for the ACB versus ARS, and 0.62 for the ADS versus ARS. Mean TSDD was 0.50 (± 1.58) for the DBI-ACh and 0.20 (± 1.06) for the SAMS. Spearman's rank correlation test comparing these latter two measures was 0.50 ($p < 0.001$).

DISCUSSION

To the best of our knowledge, this is the first study to compare any anticholinergic use across all five scales. Of note, there was more than a three-fold difference in prevalence of any anticholinergic use, with the lowest (16%) identified by the SAMS medication list and the highest (51%) by the ACB. Such variation may be attributed to the sheer difference in number of medications included in each scale, from 41 in the SAMS to 122 in the ADS. Only twenty drugs were common to all five scales: amitriptyline, benztropine, chlorpheniramine, chlorpromazine, cyclobenzaprine, cyproheptadine, desipramine, dicyclomine, diphenhydramine, hydroxyzine, hyoscyamine, imipramine, meclizine, nortriptyline, olanzapine, oxybutynin, promethazine, thioridazine, tolterodine, and trifluoperazine.

Despite this range in prevalence, the rates of anticholinergic use per individual scale are comparable to those recently reported in the literature. For example, using the ACB, Fox and colleagues found that 48% of 13,000 community-dwelling and institutionalized adults at least 65 years old took one or more anticholinergic medications, close to the 51% found in the present study.¹ Similarly, a study of 70,000 Scottish elders reported 24% were taking an anticholinergic drug per the ARS, almost identical to our 23% prevalence.² Another large study using Australian pharmacy claims data among 537,387 individuals aged 65 or older found anticholinergic exposure to be 32% with the DBI-ACh and 53% with the ADS.³ These prevalence rates are of a similar magnitude to those seen in this study (29% and 43% for the DBI-ACh and ADS, respectively). Applying all four scales to pharmaceutical claims

data, Salahudeen and colleague also found similar rates of anticholinergic use.²⁰ Although we identified no studies to date examining current anticholinergic use with the 2012 Beers criteria from which the SAMS was derived, one recent study did evaluate cumulative use over a 10-year period.¹⁶

We are also among the first to compare the agreement of the three scales that do not consider dosage (ADS, ACB, and ARS) using an older community-based population. Although the present study shows only moderate concordance ($\kappa = 0.70$), this was higher than that found among older hospitalized psychiatric Spanish patients in which kappa statistics between each pairing were ACB-ARS: 0.25, ADS-ARS: 0.19, and ADS-ACB: 0.21.²¹ Possible explanations for this discrepancy include differences in the sampled patient population (community-dwelling versus hospitalized) and the inclusion of medications not available in the United States.

In our study, we found only moderate correlation ($r_s = 0.50$) between the two scales incorporating dosage (DBI-ACh and SAMS). Moreover, we found the mean TSDD to be higher with the DBI-ACh than the SAMS. However, this overall comparison may hide the importance of using geriatric versus adult minimum effective daily doses in the TSDD calculations. To examine this, post-hoc we recalculated scores for the DBI-ACh and SAMS only using the 38 drugs shared by both scales. Contrary to the primary finding, TSDD was higher for the SAMS [(0.18 (± 1.01))] than the DBI-ACh [0.08 (± 0.40)], indicating greater anticholinergic burden in older adults. Consequently, the DBI-ACh may in fact underestimate the impact of these specific drugs in a geriatric population.

With regard to the clinical applicability of these findings, it would appear that these five scales are not likely interchangeable in their application to older patients' drug regimens. This contention is supported by the findings of Kashyap and colleagues.²² They reported that application of the ADS, ACB, ARS, and DBI to older outpatient's medications each predicted worsening cognitive performance, but on different neuropsychological tests.²² Although Salahudeen found a 20% increased risk of falls-related hospitalizations with the ADS, ACB, and ARS and a 60% increased risk with the DBI-ACh, it is important to note that no direct comparison should be made between scales as these are incident rate ratios.²⁰ The SAMS was not included in these two studies, but a recent analysis using this measure did find a 54% increased risk in hazard rate for dementia in those with one standardized daily dose taken for at least three years over a 10 year period.¹⁶

As with any study of this nature, there are some limitations that must be considered. The cross-sectional study design only captures medication usage in the two-weeks prior to the baseline study visit. However, many of the included medication classes (e.g., bladder antispasmodics, tricyclic antidepressants) are typically used chronically, and thus would remain stable over time. Further, recently-published studies suggest that anticholinergic use is actually increasing over time, which would potentially further increase discordance.^{2,4} Finally, the subjects enrolled in the Health ABC study were well-functioning older adults located in two cities within the United States, which may limit generalizability to more frail or more diverse populations.

Despite these potential limitations, our study confirms there is only moderate concordance among the three anticholinergic scales that do not consider dosage and the two scales utilizing dosage when applied to community-dwelling older adults. Before any one scale can be considered the gold standard, future research is needed to examine how these differences in measurement impact their predictive validity with respect to clinically relevant outcomes, such as cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1 Participant Characteristics ($N = 3,055$).

Variables	%	Mean ($\pm$ SD)
Sociodemographics		
Black race	41.4	
Female gender	51.5	
Age		74.00 ($\pm$ 2.87)
Site (Pittsburgh)	49.6	
Education		
Postsecondary	42.2	
High school graduate	32.7	
Less than high school graduate	25.1	
Living alone	30.2	
Health status		
Excellent/good self-rated health	83.8	
Total number of medications		1.72 ($\pm$ 1.99)

Table 2

Kappa Statistics Comparing Any Anticholinergic Use Among the Five Scales.

	ACB	ARS	ADS	DBI-ACh	SAMS
ACB		0.43	0.65	0.33	0.30
ARS			0.53	0.57	0.68
ADS				0.42	0.41
DBI-ACh					0.61
SAMS					

Abbreviations: ACB = Anticholinergic Cognitive Burden Scale; ARS = Anticholinergic Risk Scale; ADS = Anticholinergic Drug Scale; DBI-ACh = anticholinergic component of the Drug Burden Index; SAMS = Summated Anticholinergic Medications Scale.

Table 3

Comparison of the Number of Participants Distributed Across Scores Categories Applying the ACB, ADS, and ARS.

	ADS ^a				ARS ^b			
	0	1-2	3	Total	0	1-2	3	Total
ACB ^c	0	1357	125	16	1498	12	1	1498
	1-2	369	511	68	948	200	15	948
	3	27	88	494	609	84	397	609
	Total	1753	724	578	3055	296	413	3055
ADS	0				1717	34	2	1753
	1-2				555	158	11	724
	3				74	104	400	578
	Total				2346	296	413	3055

^aConcordance between ADS and ACB: 0.70;

^bConcordance between ARS and ACB: 0.54.

^cConcordance between ADS and ARS: 0.62.

Abbreviations: ADS = Anticholinergic Drug Scale; ARS = Anticholinergic Risk Scale; ACB = Anticholinergic Cognitive Burden Scale.