The Anticholinergic Drug Scale as a Measure of Drug-Related Anticholinergic Burden: Associations With Serum Anticholinergic Activity

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Anticholinergic Drug Scale (ADS) scores were previously associated with serum anticholinergic activity (SAA) in a pilot study. To replicate these results, the association between ADS scores and SAA was determined using simple linear regression in subjects from a study of delirium in 201 long-term care facility residents who were not included in the pilot study. Simple and multiple linear regression models were then used to determine whether the ADS could be modified to more effectively predict SAA in all 297 subjects. In the replication analysis, ADS scores were significantly associated with SAA (R^2 = .0947, P < .0001). In the modification analysis, each model significantly predicted SAA, including ADS scores (R^2 = .0741, P < .0001). The modifications examined did not appear useful in optimizing the ADS. This study replicated findings on the association of the ADS with SAA. Future work will determine whether the ADS is clinically useful for preventing anticholinergic adverse effects.

Keywords: *Anticholinergics; serum anticholinergic activity; Anticholinergic Drug Scale*

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Anticholinergic medications are known contributors to numerous adverse events in the elderly. These events can include constipation, heat intolerance, dry eyes, dry mouth, tachycardia, urinary retention, forgetfulness, agitation, paranoia, and delirium, among others.[1] A rating scale to quantify anticholinergic burden could be useful to those providing care to elderly patients to guide interventions to reduce the risk of anticholinergic-induced adverse events. Such a scale could also be a useful research tool for examining anticholinergic use in high-risk populations, such as people with dementia. Serum anticholinergic activity (SAA), despite a number of limitations, is still considered the current gold standard in quantifying anticholinergic burden.[2] However, at present, SAA is only measured in a limited number of research laboratories. Furthermore, if SAA is determined to be elevated, this does not provide any guidance as to which drugs might be discontinued to reduce anticholinergic burden. In contrast, an anticholinergic drug rating scale could identify those at risk of adverse events and provide guidance in interventions. An anticholinergic drug rating scale for the purpose of quantifying anticholinergic burden has

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been in development through the collaboration of a number of investigators.[3] In this scale, drugs are rated in an ordinal fashion from 0 to 3, with 0 signifying no known anticholinergic activity and 3 signifying marked anticholinergic activity. Scores of all the medications a subject receives are then summed to determine a total score. The scale was previously referred to as the Clinician-Rated Anticholinergic Scale–modified version due to the origin of the rating concepts and original ratings.[4] However, the name has been changed to the Anticholinergic Drug Scale (ADS) for brevity.

In a pilot validation analysis, the ADS score was significantly associated with the SAA among the first 98 subjects in an observational study of delirium in long-term care.[3] Therefore, the first objective of the present study was to replicate this initial finding in the remaining 201 subjects who were subsequently enrolled in this study. The second objective was to determine if 2 modifications to the ADS improved its accuracy in predicting SAA. These modifications included an adjustment for individual drug dosing and the use of empirically derived weights for the 3 levels of anticholinergic potency ratings.

METHODS

Sample

Subjects were part of a 1-month, cross-sectional, observational study of delirium in rural long-term care facilities, which was approved by the University of Iowa Institutional Review Board.[5] The present study is a secondary analysis of data from the delirium study. The analysis was done to help determine optimal methods for estimating anticholinergic burden using medication lists. For the delirium study, long-term care facilities were selected at random from a geographic catchment area, and subjects were randomly selected within these facilities. Consent of the facility as well as the subject or a family member or guardian was required for inclusion. Other inclusion criteria included the ability to read, write, and speak English and admission to a skilled or intermediate care unit for at least 30 days. Exclusion criteria included the presence of an implanted defibrillator, surgical alteration of the urinary tract or urinary bladder, and an admitting diagnosis of psychosis, head trauma, conditions resulting in increased intracranial pressure, toxin-related neurologic disorders, or delirium at the screening visit. Persons who were delirious upon initial assessment were also excluded.

Measurement of SAA

Serum for the determination of SAA was drawn on day 14, the midpoint of the study, in those subjects who were present at the facility and allowed a blood draw on that day. It was then stored at –20°C until assayed using the methods first described by Tune and Coyle.[6] A radioreceptor assay was used, which measures the specific binding of tritiated quinuclidinyl benzilate (3H-QNB, a potent anticholinergic compound) to rat muscarinic brain receptors in the presence of serum. Substances in the serum with affinity for muscarinic receptors, including anticholinergic substances, compete for muscarinic binding sites with 3H-QNB. Atropine is used as a reference compound by measuring its propensity to displace 3H-QNB at various concentrations. The results of the assay are expressed in atropine equivalents (picomole/milliliter). These values represent the amount of atropine that would need to be placed in a 1-mL sample of serum with no baseline anticholinergic activity to achieve the same displacement of 3H-QNB from the muscarinic receptors. In previous research, values have been expressed in a variety of units, including pmol/0.2 mL and others. The units picomole/milliliter are used here because of a movement to standardize the reporting of SAA to said units.

ADS Scores

Medication lists were determined based on subjects' chronic medications and as-needed medications received on the day before the SAA blood draw or before 6 AM on the day of the blood draw (blood was drawn in the morning after 6 AM). The anticholinergic potency of each medication was rated using the ADS.[3] Ratings on the ADS are defined as follows: level 0 = no known anticholinergic properties; level 1 = potentially anticholinergic as evidenced by receptor binding studies; level 2 = anticholinergic adverse events sometimes noted, usually at excessive doses; and level 3 = markedly anticholinergic. Drugs rated level 1, 2, or 3 are listed in the appendix. A listing of level 0 drugs is available in a separate appendix available online at http://jcp.sagepub.com/supplemental. ADS total scores were determined by summing the ratings of all drugs received by a subject. If a drug was received as a scheduled medication and also as an as-needed medication, its rating was included twice.

Adjustment for Doses

The potential contribution of dose was assessed by refiguring a score using a dose-adjustment strategy for level 2 and 3 anticholinergics. First, the maximum recommended daily dose for each agent was determined based on the product labeling approved by the Food and Drug Administration in the United States. No special dosing recommendations for geriatric patients were considered, because older drugs were unlikely to include these recommendations in the labeling and consistency was desired. For scheduled medications, the maximum recommended daily dose was compared to each subject's total daily dose of that drug. For as-needed medications, the maximum recommended daily dose was compared to a single as-needed dose of the drug. If the dose was less than or equal to one third of the maximum recommended daily dose, the dose weight was 1. If it was greater than one third but less than or equal to two thirds of the maximum recommended daily dose, the dose weight was 2. If it was greater than two thirds and less than or equal to the maximum recommended daily dose, the dose weight was 3. Last, if it was greater than the maximum recommended daily dose, the dose weight was 4. The drug's ADS rating was then multiplied by the dose weight to determine a dose-adjusted ADS score. For example, if a level 2 anticholinergic was given at half the maximum recommended daily dose (dose weight = 2), it would contribute a score of 4. All level 1 drugs were considered to contribute a score of 1, regardless of dose. The dose-adjusted scores for all drugs received by a given subject were then summed to determine a total dose-adjusted score for that subject.

Statistical Analysis

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

Replication analysis. To replicate the previously reported pilot study results, subjects were those persons who were not included in the pilot study.[3] Simple linear regression was used to examine the association between ADS total scores and SAA.

Modification analysis. The modification analysis included subjects from the pilot study[3] and from the replication analysis in this article. Three potential linear regression models were assessed to determine whether modification of the ADS would improve its association with SAA. In model 1, simple linear regression was used to evaluate the association between ADS scores and SAA. In model 2, the dose-adjusted total scores, as described above, were used as a predictor of SAA in a simple linear regression model. Model 3 was used to examine whether the current weighting strategy used for the ADS appeared appropriate, because the level 1, 2, and 3 weightings are ordinal but not necessarily based on proportional increases in anticholinergic activity. In this model, the numbers of level 1, level 2, and level 3 anticholinergics were entered as separate variables in a multiple linear regression model, such that the relative association of each with SAA could be determined. If the apparent contribution of level 3 drugs to SAA was 8 times that of level 1 drugs, for example, this may indicate that level 3 drugs should be scored as 8 rather than as 3. Parameter estimates and confidence intervals were calculated for each level of drug to determine whether a 1, 2, or 3 proportion was consistent with the estimated contribution of anticholinergic drugs given these respective ratings.

Outliers. Data points with studentized residuals >3.3 in the linear regression analyses (corresponding to $P < .001$ compared to the value predicted by the model) were considered outliers and excluded. For the modification analyses, residuals from model 1 were used to determine outliers.

RESULTS

Replication Analysis

The replication analysis included 201 subjects, 77% (155 of 201) of whom were women, with a mean age of 86 years (SD, 7; range, 64-102 years). One subject had been determined to be an outlier and was not included. The median SAA in this sample was 1.15 pmol/mL atropine equivalents (interquartile range, 0.5-2.0; range, 0-12.3). The median ADS total score was 2 (interquartile range, 1-4; range 0-11). Simple linear regression determined that ADS total scores were significantly associated with SAA ($F = 20.82$, $df = 1$, $P < .0001$). ADS total scores explained 9.5% of the variance in SAA ($R^2 = .0947$).

Modification Analysis

The modification analysis included 297 subjects, 78% (231 of 297) of whom were women, with a mean age of 86 years (SD, 7; range, 64-106 years). Three of the original 300 subjects in whom SAA was measured were outliers and were not included in the

analysis. The median SAA was 1.80 (interquartile range, 0.70-3.70; range, 0-13.05) pmol/mL atropine equivalents. The mean number of medications received was 8.5 (SD, 3.7; range, 0-21). The mean number of medications that were rated level 0 on the ADS was 6.5 (SD, 3.1; range, 0-17). The mean number of anticholinergic medications was 2.0 (SD, 1.4; range, 0-6). Thirty-seven subjects received no anticholinergic medications. The median ADS total score was 2 (interquartile range, 1-4; range, 0-11). The median ADS total dose-weighted score was 3 (interquartile range, 1-5; range, 0-25).

Table I details the results of the linear regression models. In model 1, traditionally determined total ADS scores were significantly associated with SAA and explained just over 7% of the variance. In model 2, dose-weighted ADS scores were significantly associated with SAA, though they did not improve on the amount of variance explained with traditional ADS scores. Model 3, which created empirically derived parameter estimates, significantly predicted SAA (Table I). The contributions of level 1 and level 2 drugs approached but did not achieve statistical significance. The contribution of level 3 drugs was significant. Although the parameter estimates suggested a ratio of approximately 1:2:5 for the relative contribution of level 1, 2, and 3 drugs, respectively, the confidence intervals showed imprecise estimates that did not exclude the existing 1:2:3 weighting strategy (Table II). Furthermore, the amount of variance explained by model 3 did not appear to be substantially greater than that explained by model 1 (Table I), suggesting that a change in the ratios for ADS ratings would not lead to an important increase in the use of the ADS in predicting SAA.

DISCUSSION

The analyses presented here confirm previous findings on the relationship of the ADS with SAA, a validated measure of anticholinergic burden. Traditional ADS total scores (1:2:3 scores) were significantly associated with SAA in both analyses (new subjects and all subjects combined). The dose-weighting scheme for anticholinergics examined in these analyses did not lead to an important enhancement of the ability of the ADS to predict SAA. Empirically derived estimates confirmed that a 1:2:3 proportion for the scores on the ADS is reasonable. In addition, the confidence intervals for the empirically derived parameter estimates indicated a significantly greater contribution of level 3 drugs to SAA compared to level 1 drugs. This finding supports the need to separate anticholinergics into categories based on their anticholinergic potency, as opposed to simply categorizing drugs as anticholinergic or not. Overall, none of the analysis techniques explored improved on the traditional scoring methods for the ADS.

The amount of variance in SAA explained by the ADS in this study was similar to that explained in previous work, about 7%.[3] Unfortunately, neither alternative method of quantifying anticholinergic burden examined in this study led to a notable increase in the amount of variance explained. There are several possible explanations for this. First, the categorization of drugs using ADS ratings is a technique of limited precision. No matter how accurate the categorization, there will be differences in anticholinergic potencies among drugs within each category. Second, as discussed, the 1:2:3 proportions may not be ideal. However, using empirically derived estimates did not increase the amount of variance explained. This may also relate to the potency differences among drugs within each category. In addition, interindividual pharmacokinetic variability may have contributed to the lack of improvement in explanatory power, particularly in the case of the dose-adjustment method. However, because of the differences among drugs in pharmacokinetic parameters that might be important, attempting to account for these parameters would add a great deal of complexity to the scale, potentially reducing its overall utility. Furthermore, these factors could not be examined in claims data research, one of the potential applications for which this rating scale could be useful. Some factors, such as genetic differences in drug metabolism, could not be accounted for at all because these differences are not typically evaluated in clinical practice and were not evaluated in this study. A final hypothesis as to why there is so much unexplained variance is that endogenous substances may contribute to SAA; that is, it is not just measuring the anticholinergic properties of drugs. Evidence supporting this hypothesis has been previously discussed.[3]

Previously used methods for quantifying anticholinergic burden associated with medications have limitations.[7] SAA, though generally reliable and valid, is limited in part because it is not commercially available, has no clearly identified threshold value above which interventions are recommended, and does not provide guidance as to which medications should be discontinued or given at a decreased dose if it is elevated. Muscarinic binding or anticholinergic assays of individual drugs are limited in part because the concentrations tested may not reflect those used clinically and there is no easily used method to combine results from these assays to quantify anti-

Table I Linear Regression Models for Predicting Serum Anticholinergic Activity

Model	Predictor Variables	Model Statistics	R^2
1	ADS scores	F = 23.62, df = 1, P < .0001	.0741
2	Dose-weighted ADS scores	F = 23.80, df = 1, P < .0001	.0747
3	No. of level 1 drugs + no. of level 2 drugs + no. of level 3 drugs	F = 8.33, df = 3, P < .0001	.0786

ADS, Anticholinergic Drug Scale.

Table II Model 3, Empirically Derived Estimates for the Association of Anticholinergic Drug Scale Level 1, 2, and 3 Drugs With Serum Anticholinergic Activity

Predictor Variable	Parameter Estimate	95% Confidence Interval	Statistics
Intercept	1.741	1.239 to 2.243	t = 6.80, df = 1, P < .0001
Level 1 drugs	0.241	–0.001 to 0.484	t = 1.96, df = 1, P = .0510
Level 2 drugs	0.523	–0.077 to 1.122	t = 1.71, df = 1, P = .0875
Level 3 drugs	1.232	0.648 to 1.816	t = 4.15, df = 1, P < .0001

cholinergic burden. Previously used anticholinergic rating scales are limited because they are inconsistent and not based on empirical evidence. Although the ADS also has limitations, all the previously mentioned methods have been used in the attempt to develop a valid and reliable method for quantifying anticholinergic burden. Strengths of the ADS include that it has demonstrated some degree of criterion validity, in that total ADS scores are significantly associated with SAA. The ADS is also easily applied to drug lists in a clinical or research setting to determine overall drug-related anticholinergic burden and does not require specialized laboratory testing. Last, the ratings of anticholinergic potency of different drugs have the potential to help guide clinical interventions to reduce anticholinergic burden. The importance of this use has been emphasized in the most recent Beers list of drugs which experts consider potentially inappropriate for prescribing to the elderly.[8] The expert panel suggested that anticholinergics should be avoided in patients with cognitive impairment. However, the article does not provide thorough guidance as to which drugs have anticholinergic properties and should thus be avoided. The ADS could serve such a purpose.

CONCLUSION

The results of this study replicated previous work correlating ADS scores with the physiologic parameter of SAA, suggesting that the ADS may have use as a tool for assessing anticholinergic burden. Further studies are required to determine whether ADS scores are associated with clinical outcomes related to anticholinergic burden. The ability of the ADS to guide clinical interventions and improve clinical outcomes will also require confirmation in future studies.

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