The Anticholinergic Risk Scale and Anticholinergic Adverse Effects in Older Persons

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Background: Adverse effects of anticholinergic medications may contribute to events such as falls, delirium, and cognitive impairment in older patients. To further assess this risk, we developed the Anticholinergic Risk Scale (ARS), a ranked categorical list of commonly prescribed medications with anticholinergic potential. The objective of this study was to determine if the ARS score could be used to predict the risk of anticholinergic adverse effects in a geriatric evaluation and management (GEM) cohort and in a primary care cohort.

Methods: Medical records of 132 GEM patients were reviewed retrospectively for medications included on the ARS and their resultant possible anticholinergic adverse effects. Prospectively, we enrolled 117 patients, 65 years or older, in primary care clinics; performed medication reconciliation; and asked about anticholinergic adverse effects. The relationship between the ARS score and the risk of anticholinergic adverse effects was assessed using Poisson regression analysis.

Results: Higher ARS scores were associated with increased risk of anticholinergic adverse effects in the GEM cohort (crude relative risk [RR], 1.5; 95% confidence interval [CI], 1.3-1.8) and in the primary care cohort (crude RR, 1.9; 95% CI, 1.5-2.4). After adjustment for age and the number of medications, higher ARS scores increased the risk of anticholinergic adverse effects in the GEM cohort (adjusted RR, 1.3; 95% CI, 1.1-1.6; *c* statistic, 0.74) and in the primary care cohort (adjusted RR, 1.9; 95% CI, 1.5-2.5; *c* statistic, 0.77).

Conclusion: Higher ARS scores are associated with statistically significantly increased risk of anticholinergic adverse effects in older patients.

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THE POPULATION OF THE United States is aging rapidly, and the number of persons older than 65 years will double to 70 million by 2030.[1] Providing medical care for the aging patient presents challenges because these patients are at risk of comorbidities and polypharmacy.[2] Patients older than 65 years are prescribed a mean of 6 medications.[3] Age-related pharmacokinetic and pharmacodynamic changes increase the risk of adverse effects and interactions.[4,5]

Although treatment guidelines such as the Beers criteria can be used to identify medications that are considered inappropriate in adults older than 65 years,[6] 12% to 21% of older patients in the United States use such agents.[7,8] Medications with anticholinergic properties have frequently been cited in the literature as causing an increase in adverse events.[9,10] Such conditions often lead to consequences such as falls, impulsive behavior, and loss of independence.[11,12] Higher rates of cognitive dysfunction and delirium are found in patients experiencing a greater anticholinergic load.[12-17] Most importantly, the reduction of anticholinergic medications may be a modifiable risk factor to avoid associated morbidity.

In response to this, we developed the Anticholinergic Risk Scale (ARS), which is a tool for estimating the extent to which an individual patient may be at risk of anticholinergic adverse effects that can lead to cognitive dysfunction and delirium. The ARS ranks medications for anticholinergic potential on a 3-point scale (0, no or low risk; 3, high anticholinergic potential). The ARS score for a patient is the sum of points for his or her number of medications.

The objective of this study was to validate the ARS score against clinical symptoms of anticholinergic toxic reactions in a retrospective geriatric evaluation and management (GEM) cohort and also in a prospective older primary care population. We hypothesized that (1) the ARS score would be positively associated with the risk of anticholinergic symptoms; (2) central adverse effects (falls, dizziness, and confusion) would be more prevalent among the GEM cohort than among the

primary care cohort, attributable to the fact that the GEM cohort had more cognitive impairment and increased sensitivity to anticholinergic medications[10]; and (3) the GEM and primary care cohorts would be equally susceptible to peripheral adverse effects (dry mouth, dry eyes, and constipation), and the ARS would identify increased risk of peripheral adverse effects similarly in both cohorts.

METHODS

SUBJECTS

This study enrolled 2 cohorts of patients. The retrospective cohort consisted of 132 participants, 65 years or older, seen consecutively in GEM clinics at the Veterans Affairs Boston Healthcare System from July 1, 2004, to March 31, 2005. Multidisciplinary GEM clinics conducted patient and family interviews by a geriatrician (J.L.R.), nurse practitioner, social worker, and pharmacist (M.J.S. and M.C.A.). The pharmacist performed medication reconciliation based on the electronic medical record and the patient's presentation of medications or a medication list. The prospective cohort comprised 117 male subjects, 65 years or older, who were attending primary care clinics at the Veterans Affairs Boston Healthcare System from September 1, 2005, to June 30, 2006. We selected male subjects because of the predominance of men in our population and the high proportion of men in our retrospective cohort. Subjects in the prospective cohort provided written informed consent. The Veterans Affairs Boston Healthcare System institutional review board and research and development review committees approved the protocols.

DEVELOPMENT OF THE ARS

The 500 most prescribed medications within the Veterans Affairs Boston Healthcare System were reviewed independently by 1 geriatrician (J.L.R.) and by 2 geropharmacists (M.J.S. and M.C.A.) to identify medications with known potential to cause anticholinergic adverse effects. Topical, ophthalmic, otologic, and inhaled medication preparations were excluded from review. All medications generated by these reviews were (1) entered into the National Institute of Mental Health psychoactive drug screening program *Ki*Bank database[18] to determine the dissociation constant (pK_i) for the cholinergic receptor; (2) input into Micromedex (Thomson Micromedex, Greenwood Village, Colorado), an evidence-based review of all Food and Drug Administration–prescribed medications, to determine rates of anticholinergic adverse effects compared with placebo; and (3) searched via MEDLINE to identify medical literature related to anticholinergic adverse effects. The 3 panel members were given the available information, and they ranked the identified medications on a scale of 0 to 3 according to anticholinergic potential (0; limited or none; 1, moderate; 2, strong; and 3, very strong). There was strong agreement with respect to the medications included on the list among the reviewers (κ range, 0.85-0.89; $P<.001$) and in the agreement among ARS medication rankings (r range, 0.70-0.83; $P<.01$). In the event of a disagreement, the median ranking was used to rank the medication. An individual's ARS score was calculated as the sum of the ARS rankings assigned for each of the medications that the patient was taking, as determined by medication reconciliation.

ANTICHOLINERGIC ADVERSE EFFECTS

As part of the standard interview in the GEM clinics, a comprehensive geriatric review of systems that are documented in the medical record was conducted among participants. This review of systems identified anticholinergic adverse effects, including falls, dry mouth, dry eyes, dizziness, confusion, and constipation. In the prospective cohort study, a modified review of systems (20 questions) that included the same adverse effects was conducted among the primary care patients. We assigned 1 point for each adverse effect and used the summed number of anticholinergic adverse effect points in our analysis. To better capture the nature of the adverse effects and to evaluate our second hypothesis, we categorized the anticholinergic adverse effects as central effects (falls, dizziness, and confusion) and as peripheral effects (dry mouth, dry eyes, and constipation).

COVARIATES

From the electronic medical record, we collected information on patient age and serum creatinine level. Age was collected because of the increased anticholinergic medication use and subsequent anticholinergic adverse effects associated with age.[10] Serum creatinine level was collected because decreased renal function can affect drug excretion. From the medication reconciliation, we counted the total number of medications that the patient was taking, excluding topical, ophthalmic, otologic, and inhaled medications. The total number of medications prescribed has been used as a surrogate for medical comorbidity.[19]

STATISTICAL ANALYSIS

Data on medications and adverse effects were collected by geriatric pharmacy residents who were blinded to the ARS groupings and study aims. All statistical analyses were performed using commercially available software (STATA SE version 9.1; StataCorp LP, College Station, Texas).

The GEM and primary care cohorts were compared using t test for continuous variables and χ^2 test for dichotomous and ordinal variables. Our primary exposure was the ARS score for a patient. Our primary outcome was the count of anticholinergic adverse effects. Because our exposure and outcome variables were not normally distributed, we categorized the participants in both cohorts into the following 3 groups: (1) those with an ARS score of 0 (no ARS medications), (2) those with an ARS score or 1 or 2, and (3) those with an ARS score of 3 or higher. The anticholinergic adverse effect count was compared with and within these ARS groups using χ^2 test.

Because our exposure and outcome variables did not conform to a normal distribution, we selected Poisson regression for unadjusted and multivariate analysis. Poisson regression analysis is preferred for nonnormal data when the primary outcome variable is a nonnegative count. From this analysis, we reported the risk of anticholinergic adverse effects with increasing ARS score. Multivariate modeling adjusted for age and for the total number of medications and was used to calculate the c statistic for model discrimination. Poisson model fit was determined using the deviance statistic.

RESULTS

Table 1 gives the characteristics of the retrospective GEM cohort and of the prospective primary care cohort. As expected, the GEM patients were older than the primary care patients. Serum creatinine levels were similar in the 2 cohorts. The GEM patients were taking statistically significantly fewer medications than the primary care patients (mean [SD], 7.9 [2.8] vs 9.0 [4.5]; $P=.05$). However, the ARS scores were higher among the GEM patients (mean [SD], 1.4 [1.9] vs 0.7 [1.2]). The ARS scores were

Table 1. Baseline Characteristics of the Cohorts

Characteristic	Retrospective Geriatric Evaluation and Management Cohort (n=132)	Prospective Primary Care Cohort (n=117)	*P* Value
Age, mean (SD), y	78.7 (5.3)	71.5 (11.6)	<.001
Male sex, No. (%)	128 (97.0)	117 (100.0)	.99
Creatinine level, mean (SD), mg/dL	1.2 (0.4)	1.2 (0.4)	.24
No. of medications, mean (SD)	7.9 (2.8)	9.0 (4.5)	.05
Anticholinergic Risk Scale score, No. (%)			<.01
0	70 (53.0)	82 (70.1)	
1-2	32 (24.2)	26 (22.2)	
≥3	30 (22.7)	9 (7.7)	
Anticholinergic adverse effects, mean (SD)[a]	1.5 (1.4)	1.1 (1.1)	.01
Central, No. (%)			
Falls	53 (40.2)	14 (12.0)	<.001
Dizziness	33 (25.0)	8 (6.8)	.17
Confusion	51 (38.6)	14 (12.0)	<.001
Peripheral, No. (%)			
Dry mouth	14 (10.6)	52 (44.4)	<.001
Dry eyes	18 (13.6)	6 (5.1)	.02
Constipation	32 (24.2)	36 (30.8)	.39

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a]The anticholinergic adverse effect data were nonnormal, and the 2 cohorts were compared using Mann-Whitney rank sum test.

not normally distributed, and the primary care patients were less likely to be taking medications listed on the ARS. The GEM patients were more likely to report central adverse effects, including falls, dizziness, and confusion, than the primary care patients, although dizziness did not reach statistical significance. Compared with the GEM cohort, the primary care cohort reported dry mouth more frequently, dry eyes less frequently, and constipation about equally.

Table 2 gives the numbers of anticholinergic adverse effects associated with ARS scores of 0, 1 to 2, and 3 or higher. Among both cohorts, the prevalences and numbers of anticholinergic adverse effects statistically significantly increased with higher ARS scores ($P<.001$ for both). This is initial evidence of a dose-response relationship. In both cohorts, when the total ARS score was 3 or higher, 70% or more of the patients reported 2 or more anticholinergic adverse effects.

Table 3 gives the unadjusted risk ratios in the cohorts for the total numbers of anticholinergic, central, and peripheral adverse effects. The deviance statistic was acceptable ($P>.05$) for all models. A sensitivity analysis with continuous ARS scores and ARS groupings did not notably change the regression results; therefore, the ARS groupings are presented to improve clinical usefulness. In both cohorts, higher ARS scores were associated with increased risk of anticholinergic adverse effects (GEM cohort crude RR, 1.5; 95% CI, 1.3-1.8 vs primary care cohort crude RR, 1.9; 95% CI, 1.9-2.4). Both cohorts had similar risks of peripheral adverse effects (GEM cohort crude RR, 1.6; 95% CI, 1.2-2.2 vs primary care cohort crude RR, 2.1; 95% CI, 1.6-2.8). Higher ARS scores were associated with increased risk of central adverse effects in the GEM patients (GEM cohort crude RR, 1.5; 95% CI, 1.3-1.8 vs primary care cohort crude RR, 1.3; 95% CI, 0.8-2.1). After adjustment for age and the total number of medications, higher ARS scores statistically significantly increased the risk of anticholinergic adverse effects in both cohorts (GEM cohort adjusted RR, 1.3; 95% CI, 1.1-1.6 vs primary care cohort adjusted RR, 1.9; 95% CI, 1.5-2.5), and there was good model discrimination (GEM cohort *c* statistic, 0.74; primary care cohort *c* statistic, 0.77).

COMMENT

Consistent with our primary hypothesis, this study found that the ARS score was reliably associated with the risk of anticholinergic adverse effects in GEM patients and in older primary care patients after adjustment for age and the total number of medications. The GEM patients described more central adverse effects than the primary care patients. After adjustment for age and the number of medications, higher ARS scores were associated with increased risk of central adverse effects in the GEM cohort but not in the primary care cohort. In the primary care patients, ARS scores were associated with the adjusted risk of peripheral adverse effects.

Because older patients have increased susceptibility to anticholinergic toxic effects of medications, the assessment of toxic reactions is crucial in older populations. Our findings are consistent with other studies that created ranked lists of anticholinergic medications and associated these with clinical outcomes. Han et al[17] used similar methods to develop a ranked list of anticholinergic medications that were positively correlated with delirium severity in medical inpatients. The present study is similar because our outcome was clinical adverse effects from anticholinergic medications. However, our study expands the ranked list to older outpatients in GEM and primary care settings.

More recently, studies examined the association of the ranked list with serum anticholinergic activity. Serum anticholinergic activity measures in vitro muscarinic affinity and has been improved to include cholinergic receptor subtypes.[20] Carnahan et al[21] described the correlation between the Anticholinergic Drug Scale and serum anticholinergic activity in patients receiving long-term care. Unfortunately, although serum anticholinergic activity has been associated with delirium, cognitive performance, and the use of antipsychotic medications,[9,10,13,22] the measurement of serum anticholinergic activity is expensive; it is not readily available to most practitioners across health care settings; and timely interpretation of the results in clinical practice is challenging.[23]

In the GEM cohort, the adjusted ARS score was associated with the risk of central adverse effects. The GEM patients, who are frequently referred for cognitive complaints, were more likely to report central adverse effects than the primary care cohort. Patients with dementia are more susceptible to the effects of anticholinergic

Table 2. Increased Anticholinergic Adverse Effects Associated With Higher Anticholinergic Risk Scale Scores

Anticholinergic Risk Scale Score	No. of Anticholinergic Adverse Effects, No. (%)				*P* Value[a]	
	0	1	2	≥3	Between Group	Overall
Retrospective geriatric evaluation and management cohort						<.001
0 (n=70)	26 (37.1)	26 (37.1)	13 (18.6)	5 (7.1)		
1-2 (n=32)	7 (21.9)	7 (21.9)	8 (25.0)	10 (31.3)	.006[b]	
≥3 (n=30)	1 (3.3)	5 (16.7)	12 (40.0)	12 (40.0)	.12[c]	
Prospective primary care cohort						<.001
0 (n=82)	41 (50.0)	27 (32.9)	12 (14.6)	2 (2.4)		
1-2 (n=26)	2 (7.7)	8 (30.8)	13 (50.0)	3 (11.5)	<.001[b]	
≥3 (n=9)	1 (11.1)	1 (11.1)	2 (22.2)	5 (55.6)	.05[c]	

[a] χ^2 Test.
[b] Comparing Anticholinergic Risk Scale score of 0 vs 1 to 2.
[c] Comparing Anticholinergic Risk Scale score of 1 to 2 vs 3 or higher.

medications and are more likely to receive them.[16] Unfortunately, adjustment for cognitive impairment was impossible in this study but might have provided information about the contribution of anticholinergic medications to dementia. We can only conclude that those patients referred for GEM evaluation are at increased risk of central adverse effects.

Among older primary care patients, the ARS score was associated with the risk of peripheral adverse effects. This may have resulted from (1) increased function in these patients; (2) less cognitive impairment, resulting in more accurate history taking; (3) lower prevalence of central adverse effects, which may have resulted in increased reporting of peripheral adverse effects; or (4) addition of the pharmacy team to ask about anticholinergic adverse effects, also leading to increased reporting of peripheral adverse effects.

Overall, the ARS score was associated with the risk of central and peripheral adverse effects. Although the prevalence of anticholinergic adverse effects cannot be fully explained using the ARS score, the clinical findings represent an opportunity to improve care among older patients. For example, a single medication with an ARS score of 3 would likely cause 2 or more anticholinergic adverse effects in more than 70% of the patients in the GEM and primary care cohorts.

There are several strengths to our study. First, the measurement of ARS score and anticholinergic adverse effects in a retrospective cohort and in a prospective cohort improves the generalizability of the study. Second, there was good agreement among the experts in the selection of medications for the ARS and good correlation in the ranking of medications on the ARS. Third, the electronic medical record, which included pharmacy records, allowed us to perform comprehensive medication reconciliation. Fourth, the blinding of the data collectors to the ARS improves the validity of our findings. Fifth, our results persisted after adjusting for potential confounders, including age and the number of medications.

Our study has weaknesses that require mentioning. Although calculating the ARS score is not difficult (**Table 4**), completing the ARS during the individual patient encounter is less practical compared with asking 6 questions about anticholinergic adverse effects. Therefore, we believe that there are 2 primary uses for the ARS. First, the ARS is a useful tool to identify patients at risk of anticholinergic toxic reactions in large patient databases such as those of a hospital, nursing home, health system, rehabilitation center, or pharmacy benefit manager. Prophylactic pharmacy intervention clinics designed to reduce anticholinergic exposure could minimize potential anticholinergic toxic reactions. Second, the ARS would be a useful educational aid for clinicians to identify medications with anticholinergic adverse effects so that they might avoid prescription.

In addition, this work focused on the presence or absence of anticholinergic adverse effects without regard to potential causes. By no means does the ARS score replace the decision making of the clinician. However, the statistically significantly increased risk of anticholinergic adverse effects associated with higher ARS scores suggests that medications on the ARS have a partial role in the prevalence of these adverse effects among our cohorts. Furthermore, our study treated anticholinergic ad-

Table 3. Relative Risk of Increased Anticholinergic Adverse Effects Associated With Higher Anticholinergic Risk Scale Scores

Adverse Effects	Relative Risk (95% Confidence Interval)		c Statistic
	Crude	Adjusted[a]	
Retrospective geriatric evaluation and management cohort[b]			
Anticholinergic	1.5 (1.3-1.8)	1.3 (1.1-1.6)	0.74
Central	1.5 (1.3-1.8)	1.4 (1.1-1.7)	0.74
Peripheral	1.6 (1.2-2.2)	1.4 (1.0-1.9)	0.69
Prospective primary care cohort			
Anticholinergic	1.9 (1.5-2.4)	1.9 (1.5-2.5)	0.77
Central	1.3 (0.8-2.1)	1.4 (0.8-2.3)	0.59
Peripheral	2.1 (1.6-2.8)	2.1 (1.5-2.9)	0.80

[a] For age and the number of medications.
[b] Central adverse effects include falls, dizziness, and confusion; peripheral adverse effects include dry mouth, dry eyes, and constipation.

Table 4. Anticholinergic Risk Scale[a]

3 Points	2 Points	1 Point
Amitriptyline hydrochloride	Amantadine hydrochloride	Carbidopa-levodopa
Atropine products	Baclofen	Entacapone
Benztropine mesylate	Cetirizine hydrochloride	Haloperidol
Carisoprodol	Cimetidine	Methocarbamol
Chlorpheniramine maleate	Clozapine	Metoclopramide hydrochloride
Chlorpromazine hydrochloride	Cyclobenzaprine hydrochloride	Mirtazapine
Cyproheptadine hydrochloride	Desipramine hydrochloride	Paroxetine hydrochloride
Dicyclomine hydrochloride	Loperamide hydrochloride	Pramipexole dihydrochloride
Diphenhydramine hydrochloride	Loratadine	Quetiapine fumarate
Fluphenazine hydrochloride	Nortriptyline hydrochloride	Ranitidine hydrochloride
Hydroxyzine hydrochloride and hydroxyzine pamoate	Olanzapine	Risperidone
Hyoscyamine products	Prochlorperazine maleate	Selegiline hydrochloride
Imipramine hydrochloride	Pseudoephedrine hydrochloride–triprolidine hydrochloride	Trazodone hydrochloride
Meclizine hydrochloride	Tolterodine tartrate	Ziprasidone hydrochloride
Oxybutynin chloride		
Perphenazine		
Promethazine hydrochloride		
Thioridazine hydrochloride		
Thiothixene		
Tizanidine hydrochloride		
Trifluoperazine hydrochloride		

[a] To calculate the Anticholinergic Risk Scale score for a patient, identify medications the patient is taking and add the total points for each medication.

verse effects as numerically equivalent, but in clinical practice there may be variable affects of anticholinergic adverse effects on patient health and function. The ARS also did not include topical, ophthalmic, otologic, and inhaled preparations. Although these medications may have been absorbed systemically and caused anticholinergic adverse effects, exclusion of these would have increased the reporting of anticholinergic adverse effects without increasing the ARS score. As a result, our findings may underestimate the usefulness of the ARS score in predicting reported adverse effects. Also, our sample of veterans is predominantly male, and the clinical effects of the ARS scores among women requires further study. Despite our objective methods for determining the ranking of medications on the ARS, there remains room for debate. Finally, the most prescribed medications at our facility may not include all potentially anticholinergic medications. As listed in Table 4, the ARS includes medications similar to those in other published scales,[21,24] and many medications that are considered inappropriate in older persons are included.[6]

CONCLUSIONS

Adverse effects related to anticholinergic medication use can have negative effects in older patients. The ARS is a categorically ranked list of medications that predicted increased risk of anticholinergic adverse effects in older patients. We believe that these findings have implications in the identification of older patients at risk of anticholinergic toxic reactions across a spectrum of care settings. Once identified using the ARS, proactive interventions could reduce complications and preserve functioning. Further study of the effectiveness of such a program is warranted.

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