The Anticholinergic Risk Scale and Anticholinergic Adverse Effects in Older Persons

James L. Rudolph, MD, SM; Marci J. Salow, PharmD; Michael C. Angelini, MA, PharmD; Regina E. McGlinchey, PhD

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; p statistic, 0.74) and in the primary care cohort (adjusted RR, 1.9; 95% CI, 1.5-2.5; p statistic, 0.77).

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

Arch Intern Med. 2008;168(5):508-513
primary care cohort, attributable to the fact that the GEM cohort had more cognitive impairment and increased sensitivity to anticholinergic medications, 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 geroparmacists (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 KiBank database to determine the dissociation constant (pKᵦ) 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 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. 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.

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 χ² 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 of 1 or 2, and (3) those with an ARS score of 3 or higher. Anticholinergic adverse effect count was compared with and within these ARS groups using χ² 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 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
more anticholinergic adverse effects.

In both cohorts, when the total ARS score was
significantly increased with higher ARS scores
(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 ad-
verse 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 statisti-
cally significantly increased the risk of anticholinergic ad-
verse 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 dis-
tribution (GEM cohort c statistic, 0.74; primary care cohort

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 ad-
verse effects, including falls, dizziness, and confusion, than
the primary care patients, although dizziness did not reach
statistical significance. Compared with the GEM co-
hort, the primary care cohort reported dry mouth more
frequently, dry eyes less frequently, and constipation about
equally.

Table 2 gives the numbers of anticholinergic ad-
verse 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 evident evidence of a dose-response rela-
tionship. 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 co-
horts for the total numbers of anticholinergic, central,
and peripheral adverse effects. The deviance statistic was
acceptable (P > .05) for all models. A sensitivity analy-
sis with continuous ARS scores and ARS groupings did
not 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).

Table 1. Baseline Characteristics of the Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Retrospective Geriatric Evaluation and Management Cohort (n=132)</th>
<th>Prospective Primary Care Cohort (n=117)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>78.7 (5.3)</td>
<td>71.5 (11.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>128 (97.0)</td>
<td>117 (100.0)</td>
<td>.99</td>
</tr>
<tr>
<td>Creatinine level, mean (SD), mg/dL</td>
<td>1.2 (0.4)</td>
<td>1.2 (0.4)</td>
<td>.24</td>
</tr>
<tr>
<td>No. of medications, mean (SD)</td>
<td>7.9 (2.8)</td>
<td>9.0 (4.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Anticholinergic Risk Scale score, No. (%)</td>
<td>7.9 (2.8)</td>
<td>9.0 (4.5)</td>
<td>.05</td>
</tr>
<tr>
<td>Total number of medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central, No. (%)</td>
<td>31 (23.8)</td>
<td>34 (29.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Falls</td>
<td>53 (40.2)</td>
<td>42 (35.6)</td>
<td>.17</td>
</tr>
<tr>
<td>Dizziness</td>
<td>33 (25.0)</td>
<td>26 (22.2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Confusion</td>
<td>51 (38.6)</td>
<td>42 (35.6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peripheral, No. (%)</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>.39</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>GEM Cohort (n=132)</th>
<th>Primary Care Cohort (n=117)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>51 (38.6)</td>
<td>42 (35.6)</td>
<td>&lt;.01</td>
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<tr>
<td>Dizziness</td>
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<td>Falls</td>
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<td>42 (35.6)</td>
<td>.17</td>
</tr>
<tr>
<td>Constipation</td>
<td>32 (24.2)</td>
<td>36 (30.8)</td>
<td>.39</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>18 (13.6)</td>
<td>6 (5.1)</td>
<td>.02</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (24.2)</td>
<td>36 (30.8)</td>
<td>.39</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (24.2)</td>
<td>36 (30.8)</td>
<td>.39</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Nervousness</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Peripheral adverse effects</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Vision disturbance</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Urinary hesitancy</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>14 (10.6)</td>
<td>36 (30.8)</td>
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</tr>
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</tr>
</tbody>
</table>

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

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

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 co-
hort but not in the primary care cohort. In the primary care patients, ARS scores were associated with the ad-
justed risk of peripheral adverse effects.

Because older patients have increased susceptibility
to anticholinergic toxic effects of medications, the as-
essment of toxic reactions is crucial in older popula-
tions. Our findings are consistent with other studies that
created ranked lists of anticholinergic medications and
associated these with clinical outcomes. Han et al17 used
similar methods to develop a ranked list of anticholin-
ergic medications that were positively correlated with del-
irium severity in medical inpatients. The present study
is similar because our outcome was clinical adverse ef-
ffects 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 ant-
icholinergic activity measures in vitro muscarinic affin-
ity and has been improved to include cholinergic recep-
tor subtypes.20 Carnahan et al21 described the correlation
between the Anticholinergic Drug Scale and serum an-
ticholinergic activity in patients receiving long-term care.
Unfortunately, although serum anticholinergic activity
has been associated with delirium, cognitive perform-
ance, and the use of antipsychotic medications,9,10,13,22
the measurement of serum anticholinergic activity is ex-
pensive; 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 asso-
ciated with the risk of central adverse effects. The GEM
patients, who are frequently referred for cognitive com-
plaints, were more likely to report central adverse ef-
facts than the primary care cohort. Patients with demen-
tia are more susceptible to the effects of anticholinergic
Although calculating the ARS score is not difficult, understanding its clinical significance is more challenging. Our study found an increased risk of adverse effects with higher ARS scores, which is consistent with previous research. This is important for both patients and providers, as it suggests that reducing anticholinergic exposure could improve patient outcomes. However, the study has weaknesses that should be considered, such as potential confounding factors and the need for adjustment for cognitive impairment.

Overall, the ARS score is a useful tool for identifying patients at risk of anticholinergic adverse effects. It can guide decision-making in clinical practice, and advocate for changes in the healthcare system, to reduce exposure to anticholinergic medications.
verse effects as numerically equivalent, but in clinical practice there may be variable effects 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 require 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, and many medications that are considered inappropriate in older persons are included.

Table 4. Anticholinergic Risk Scalea

<table>
<thead>
<tr>
<th>3 Points</th>
<th>2 Points</th>
<th>1 Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline hydrochloride</td>
<td>Amantadine hydrochloride</td>
<td>Carbipoda-levodopa</td>
</tr>
<tr>
<td>Atropine products</td>
<td>Baclofen</td>
<td>Entacapone</td>
</tr>
<tr>
<td>Benzodione mesylate</td>
<td>Cetirizine hydrochloride</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>Cimetidine</td>
<td>Methocarbamol</td>
</tr>
<tr>
<td>Chlorpheniramine maleate</td>
<td>Clozapine</td>
<td>Metoclopramide hydrochloride</td>
</tr>
<tr>
<td>Chlorpromazine hydrochloride</td>
<td>Cyclcophenazine</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>Cyproheptadine hydrochloride</td>
<td>Desipramine</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Dicyclomine hydrochloride</td>
<td>Diapramine</td>
<td>Hydrochloride</td>
</tr>
<tr>
<td>Diphenhydramine hydrochloride</td>
<td>Loratadine</td>
<td>Quetiapine fumarate</td>
</tr>
<tr>
<td>Fluphenazine hydrochloride</td>
<td>Nortriptyline</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Hydroxyzine hydrochloride and hydroxyzine pamoate</td>
<td>Olanzapine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Hyoscyamine products</td>
<td>Prochlorperazine maleate</td>
<td>Selegiline hydrochloride</td>
</tr>
<tr>
<td>Imipramine hydrochloride</td>
<td>Pseudoephedrine</td>
<td>Trazodone hydrochloride</td>
</tr>
<tr>
<td>Meprazine hydrochloride</td>
<td>Tolerodine tartrate</td>
<td>Ziprasidone hydrochloride</td>
</tr>
<tr>
<td>Oxybutynin chloride</td>
<td>Perphenazine</td>
<td>Promethazine hydrochloride</td>
</tr>
<tr>
<td>Promethazine hydrochloride</td>
<td>Trihexyline</td>
<td>Trichloroquine hydrochloride</td>
</tr>
<tr>
<td>Trazodone hydrochloride</td>
<td>Trifluoperazine</td>
<td>Trimipramine hydrochloride</td>
</tr>
</tbody>
</table>

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

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.

Accepted for Publication: September 29, 2007.
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Author Contributions: Study concept and design: Rudolph, Salow, and Angelini. Acquisition of data: Rudolph and Salow. Analysis and interpretation of data: Rudolph, Angelini, and McGlinchey. Drafting of the manuscript: Rudolph, Salow, and McGlinchey. Critical revision of the manuscript for important intellectual content: Rudolph, Salow, Angelini, and McGlinchey. Statistical analysis: Rudolph and McGlinchey. Obtained funding: Rudolph and McGlinchey. Administrative, technical, and material support: Rudolph, Salow, and McGlinchey. Study supervision: Rudolph and McGlinchey.

Financial Disclosure: Dr Angelini has consulted for Eli Lilly and has received lecture fees from Eli Lilly and AstAstraZeneca.

Funding/Sponsor: This study was supported by grant K12 AG000294-18 from the National Institute on Aging (Dr Rudolph), by grant R01 1405 from the National Institute on Alcohol Abuse and Alcoholism (Dr McGlinchey), and by a Veterans Affairs Merit Review (Dr McGlinchey).

Previous Presentation: This study was presented as a poster at the 2007 American Geriatrics Society Annual Scientific Meeting; May 4, 2007; Seattle, Washington.

Additional Contributions: Richard N. Jones, ScD, assisted with the statistical analysis. Ryann Welch, PharmD, and Ingrid Michael, PharmD, contributed to data collection and analysis.

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