

# Assessing and predicting drug-induced anticholinergic risks: an integrated computational approach

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## Abstract

**Background:** Anticholinergic (AC) adverse drug events (ADEs) are caused by inhibition of muscarinic receptors as a result of designated or off-target drug–receptor interactions. In practice, AC toxicity is assessed primarily based on clinician experience. The goal of this study was to evaluate a novel concept of integrating big pharmacological and healthcare data to assess clinical AC toxicity risks.

**Methods:** AC toxicity scores (ATSs) were computed using drug–receptor inhibitions identified through pharmacological data screening. A longitudinal retrospective cohort study using medical claims data was performed to quantify AC clinical risks. ATS was compared with two previously reported toxicity measures. A quantitative structure–activity relationship (QSAR) model was established for rapid assessment and prediction of AC clinical risks.

**Results:** A total of 25 common medications, and 575,228 exposed and unexposed patients were analyzed. Our data indicated that ATS is more consistent with the trend of AC outcomes than other toxicity methods. Incorporating drug pharmacokinetic parameters to ATS yielded a QSAR model with excellent correlation to AC incident rate ( $R^2 = 0.83$ ) and predictive performance (cross validation  $Q^2 = 0.64$ ). Good correlation and predictive performance ( $R^2 = 0.68/Q^2 = 0.29$ ) were also obtained for an M2 receptor-specific QSAR model and tachycardia, an M2 receptor-specific ADE.

**Conclusions:** Albeit using a small medication sample size, our pilot data demonstrated the potential and feasibility of a new computational AC toxicity scoring approach driven by underlying pharmacology and big data analytics. Follow-up work is under way to further develop the ATS scoring approach and clinical toxicity predictive model using a large number of medications and clinical parameters.

**Keywords:** adverse drug reactions, anticholinergic toxicity, clinical toxicology, big data, drug safety, biomedical informatics

Received: 9 June 2017; revised manuscript accepted: 19 July 2017

## Introduction

Anticholinergics (ACs), as a drug class, provide significant therapeutic benefits in a variety of disease states. Many non-AC medications, however, may also elicit AC pharmacologic responses through off-target interactions with muscarinic receptors. The clinical consequences are well documented, ranging from subtle cognitive changes to acute symptoms such as tachycardia, delirium,

hallucinations, etc.<sup>1</sup> It has been reported that up to 60% of elderly patients in primary care settings receive at least one medication that may lead to AC toxicity.<sup>2,3</sup> Given the widespread use of these medications, there is a critical need of a rational and efficient method for assessing AC risks.

A variety of AC toxicity scales have been proposed.<sup>4–9</sup> The anticholinergic risk scale (ARS)<sup>6</sup>

*Ther Adv Drug Saf*  
2017, Vol. 8(11) 361–370  
DOI: 10.1177/  
2042098617725267

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and anticholinergic cognitive burden (ACB)<sup>5</sup> assigned 0–3 toxicity scales to medications based on clinician opinion. Others measured drug–receptor dissociation constants from *in vitro* experiments.<sup>10</sup> Attempts have been made to improve the scales by adding additional drugs,<sup>11</sup> or combining several different scales.<sup>12</sup> However, none of these approaches has emerged as a gold standard for reliable AC toxicity assessment.<sup>13–17</sup> Furthermore, the plethora of AC toxicity measures attests to the need and challenges of developing a systematic, efficient, and clinically relevant AC toxicity scoring approach.

However, there is an ever-increasing wealth of freely available bioactivity and pharmacological data. The *ChEMBL21* database,<sup>18</sup> the largest bioactivity database in the world, contains more than 1.5 million small molecules, 10,000 receptors, and 14 million bioactivity records. Adopting established bioinformatics algorithms,<sup>19</sup> the vast amount of pharmacological data can be mined to identify relevant drug–receptor inhibitions (including inhibitions as a result of off-target interactions) and form the basis of computational AC toxicity scores (ATSs). Similarly, AC clinical responses can be extracted from large healthcare data such as medical insurance claims. Thus, combining pharmacological and insurance claims data may afford an efficient and noninvasive method to assess drug-induced AC toxicity. Our goal in this work is not a complete computational solution, but rather to test the feasibility of the new big data-based approach.

## Methods

### Medications

To elucidate the complex nature of drug-induced toxicity, we need to capture the molecular-level information that entails drug actions at relevant receptors. There are five muscarinic (M) receptor subtypes that are involved in AC toxicity: M1, M4, and M5 are predominantly expressed in the central nervous system (CNS); M2 is mostly found in cardiac tissue; M3 is predominantly present in the gastrointestinal tract and genitourinary tissues.<sup>20</sup> Due to funding limitations, a subset of 25 medications were selected for this pilot study (Table 1). The selection criteria include: (1) commonly prescribed; (2) representatives of eight major drug classes (antidepressants, antihistamines, anti-Parkinson's agents, antipsychotics, benzodiazepines, gastrointestinal agents, muscle

relaxants, and opioids);<sup>21</sup> and (3) mostly consistently ranked by ACB and ARS scales. It is worth noting that many of the 25 medications are not considered as classic ACs or antimuscarinics.

### Computing ATS scores

The molecular structures of the 25 medications were retrieved from *DrugBank*<sup>22</sup> and used to query the *ChEMBL21* bioactivity database using our in-house TargetSearch program (<http://dxu-lab.pharmacy.isu.edu>). *ChEMBL21* was searched for either known bioactivity between a medication and five muscarinic receptor subtypes or unknown off-target interactions *via* inferred structure-bioactivity relationships, the cornerstone of our computational ATS approach. If a query medication was found to have similar chemical structure and features to a bioactive molecule in the database, and this bioactive molecule has known bioactivity data associated with any of the five muscarinic receptors, we can infer that the medication will share similar bioactivity on the same receptors. The widely used extended connectivity fingerprints (ECFPs) or Morgan algorithm<sup>23</sup> was used in the TargetSearch program. A 10  $\mu$ M inhibitory activity cutoff was used to ensure a higher level of confidence in identifying known and inferred relationships. When a hit is found, Tanimoto coefficients<sup>24</sup> calculated by the Morgan algorithm<sup>23</sup> yield receptor-specific ATS scores, representing the drug–receptor inhibition propensity. The receptor-specific ATS scores are on a continuous scale ranging 0–1. A receptor-specific ATS score of 1 indicates a medication has known bioactivity to a muscarinic receptor whereas a score of 0 means no known or inferred interaction is found. A score between 0–1 indicates an inferred interaction is identified. The individual receptor subtype ATS scores were summed to give the total ATS score of a medication. This computational approach, illustrated in Figure 1, essentially accounts for pharmacodynamic interactions of medications. It is fast, systematic, and has been shown to effectively capture off-target interactions.<sup>21</sup>

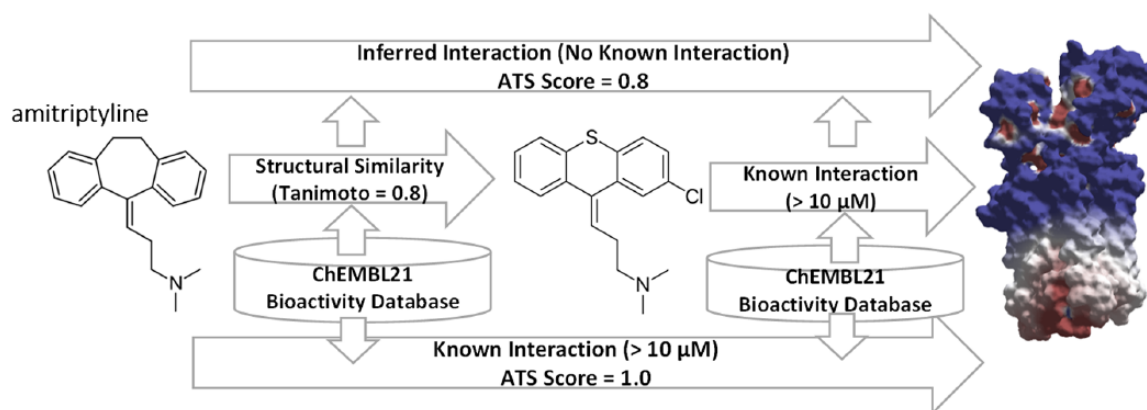
### ATS versus ACB and ARS

In order to qualitatively compare ATS with previously reported ACB and ARS scales, the ATS scores were converted from a continuous scale to an ordinal AC toxicity scale (1 = low, 2 = moderate, and 3 = high) used by ACB and ARS. Using ataxia, the most common ADE associated

**Table 1.** Selected medications and their ATS scores.

Medication	Drug class	Muscarinic receptors					Total ATS	ACB <sup>5</sup>	ARS <sup>6</sup>
		M1	M2	M3	M4	M5			
Amitriptyline	Antidepressants	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Imipramine	Antidepressants	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Brompheniramine	Antihistamines	0.75	0.43	0.43	0.75	0.75	3.11	3	NA
Carbinoxamine	Antihistamines	0.65	0.65	0.65	0.65	0.65	3.25	3	NA
Chlorpheniramine	Antihistamines	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Diphenhydramine	Antihistamines	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Benztropine	Anti-Parkinson agents	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Trihexyphenidyl	Anti-Parkinson agents	1.00	1.00	1.00	1.00	1.00	5.00	3	NA
Chlorpromazine	Antipsychotics	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Haloperidol	Antipsychotics	1.00	0.39	0.39	1.00	1.00	3.78	1	1
Perphenazine	Antipsychotics	0.78	0.78	0.78	0.78	0.78	3.90	3	3
Risperidone	Antipsychotics	1.00	1.00	1.00	1.00	1.00	5.00	1	1
Thioridazine	Antipsychotics	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Trifluoperazine	Antipsychotics	0.81	0.70	0.81	0.81	0.70	3.83	3	3
Alprazolam	Benzodiazepines	0.00	0.00	0.00	0.30	0.30	0.60	1	NA
Clorazepate	Benzodiazepines	0.34	0.34	0.34	0.34	0.34	1.70	1	NA
Diazepam	Benzodiazepines	0.40	0.40	0.40	0.40	0.40	2.00	1	NA
Atropine	Gastrointestinal agents	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Dicyclomine	Gastrointestinal agents	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Hyoscyamine	Gastrointestinal agents	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Loperamide	Gastrointestinal agents	0.49	0.49	0.49	0.49	0.49	2.45	1	2
Promethazine	Gastrointestinal agents	1.00	1.00	1.00	1.00	1.00	5.00	3	3
Ranitidine	Gastrointestinal agents	0.65	0.65	0.00	0.00	0.00	1.30	1	1
Orphenadrine	Muscle relaxants	1.00	1.00	1.00	1.00	1.00	5.00	3	NA
Fentanyl	Opioids	0.39	0.42	0.42	0.38	0.38	1.99	1	NA

ACB, anticholinergic cognitive burden; ARS, anticholinergic risk scale; ATS, anticholinergic toxicity score; NA, not available.

**Figure 1.** Schematic workflow of the computational ATS scoring approach. ATS, anticholinergic toxicity score.

**Table 2.** Demographic and clinical characteristics of the retrospective cohort.

	Exposed	Unexposed		Exposed	Unexposed
	(N = 287,614)	(N = 287,614)		(N = 287,614)	(N = 287,614)
<b>Demographic characteristics</b>			<i>Possible AC-related ADEs</i>		
Age in years (mean, SD)	37.97, 18.79	37.97, 18.79	Ataxia	20,104, 6.99%	4465, 1.55%*
(median, range)	39, 5–84	39, 5–84	Constipation	2969, 1.03%	551, 0.19%*
<65 (N, %)	268,414, 93.32	268,414, 93.32	Agitation	2027, 0.70%	601, 0.21%*
≥65 (N, %)	19,200, 6.68	19,200, 6.68	Tachycardia	1970, 0.68%	798, 0.28%*
Male (N, %)	126,376, 43.94%	126,376, 43.94%	Pupil Dilation	1436, 0.50%	978, 0.34%*
Region (N, %) South	124,538, 43.30%	76,517, 26.6%*	Fractures	1264, 0.44%	820, 0.29%*
Midwest	74,412, 25.87%	106,246, 36.94%	Syncope	979, 0.34%	302, 0.11%*
West	42,038, 14.62%	39,496, 13.73%	Hallucinations	900, 0.31%	259, 0.09%*
East	46,626, 16.21%	65,355, 22.72%	Glaucoma	745, 0.26%	1219, 0.42%*
Medicare (N, %)	10,779, 3.75%	6688, 2.33%*	Urinary retention	491, 0.17%	173, 0.06%*
<b>Clinical characteristics</b>			Delirium	277, 0.10%	77, 0.03%*
CDI (mean, SD)	1.39, 1.72	1.17, 1.59*	Dementia	165, 0.06%	124, 0.04%*
(median, range)	1.0, 0–16	1.0, 0–18	Irritability	19, 0.01%	13, 0.00%*
Charlson (mean, SD)	0.38, 1.01	0.32, 0.88*	Hypotension	137, 0.05%	45, 0.02%*
(median, range)	0, 0–17	0, 0–17	Fractures Colles	131, 0.05%	64, 0.02%*
Length of follow-up in days (mean, SD)	33.48, 108.8	33.48, 108.8	Xerostomia	41, 0.01%	15, 0.01%*
(median, range)	9.0, 1–4043	9.0, 1–4043	Confusion	16, 0.01%	6, 0.00%*
Sum of Outcomes (mean)	0.18	0.037*	Jerking	15, 0.01%	2, 0.00%*
(median, range)	0, 0–8	0, 0–8	Poisoning	1, 0.00%	0, 0.00%*

\**p* < 0.05.

AC, Anticholinergic; ADE, adverse drug event; CDI, Chronic Disease Indicator; SD, standard deviation.

with AC toxicity (Table 2) as an example, the cumulative incidence rates were summed across medications at each severity category (1–3 ordinal scale). Correlations between cumulative incidence rates and three AC toxicity scales were analyzed.

#### *Retrospective cohort study*

The *PharMetrics Legacy Health Plans Claims Data*, a de-identified longitudinal database comprising medical and pharmacy insurance claims from over 102 managed care programs, is considered representative of the United States commercially insured population.<sup>25</sup> A 10% random sample of the database (75 million unique patients) from

January 2001 through December 2013 was used to identify an exposed cohort according to the following criteria: (1) filled at least one of 25 medications (Table 1); (2) had at least 1 year of continuous health plan enrollment prior to and 3 months of continuous health plan enrollment following their earliest medication fill; (3) had no AC-related ADEs during the 180 days prior to their earliest medication fill; and (4) were aged 5 years or older at the time of their earliest medication fill. Medication exposures were assessed during each patient's follow-up period, which began with their earliest medication fill and ended when a patient had discontinued all medications (no fills within 45 days of the last fill + the last days supplied); had a gap of at least 1 month in their continuous

health plan enrollment; or the data period ended). Indicator variables (yes/no) for each of the 25 medications were used to identify patients with one or more fills of each medication.

An unexposed control cohort was extracted according to the following criteria: (1) never filled any of the 25 medications; (2) matched to patients in the exposed cohort on age, sex, and length of continuous health plan enrollment.

A total of 19 common AC-related ADEs were collected from clinical literature and compendial references.<sup>1</sup> It is worth noting that these 19 ADEs are not meant to be an exhaustive list of all potential AC-related ADEs, but represent a majority of well accepted ADEs. ICD-9-CM diagnosis codes were used to identify patients with suspected AC toxicity during the follow-up period. The first occurrence of each ADE was captured. For each patient, indicator (yes/no) variables were created for each of the 19 ADEs. The total number of distinct ADEs per patient was also calculated. To account for confounding by indication, agitation, irritability, and hallucinations were not included as eligible ADEs if a patient had any fills for antipsychotics or benzodiazepines.

Mean, standard deviation, median, and range were calculated to describe continuous clinical and demographic characteristics, while percentages were used to describe categorical characteristics. Comorbidities were assessed using the Charlson Comorbidity Index (CCI) and Chronic Disease Indicator (CDI) scores.<sup>26,27</sup> The CCI score uses medical claims to assign a comorbidity score based on the number and severity of 19 comorbid conditions. The CDI score uses medication claims to determine the number of chronic diseases. This study received institutional review board exempt status from the Idaho State University and Colorado Multiple Institutional Review Boards.

#### *Calculation of AC clinical risks*

For each of the 25 medications, the number of exposed patients and the number of ICD-9 diagnosis codes representing potential AC-related ADEs were determined. To account for potential confounding effects due to exposure to nonstudy medications and other clinical factors, the number of ADEs in the exposed cohort was adjusted by subtracting the baseline number of ADEs in

the unexposed cohort. The clinical risks of overall AC-related ADEs and tachycardia for each medication were calculated by dividing the adjusted number of ADEs from the number of exposed patients, and reported as the cumulative incidence rates per patient and per 100 patients, respectively. SAS version 9.4 and Microsoft Excel 2013 were used in data analysis.

#### *Calculation of drug absorption and distribution*

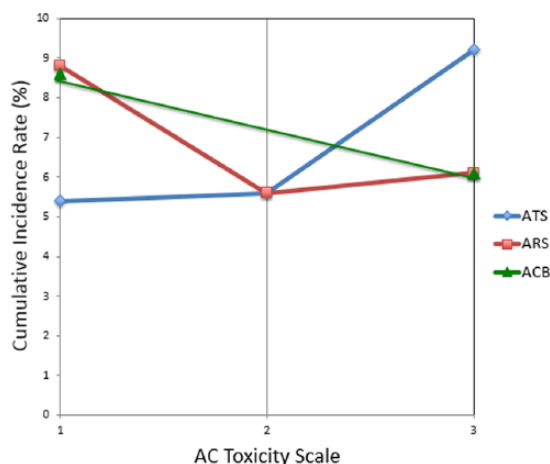
For each of the 25 medications, a set of 7 bioavailability-related parameters [molecular volume, hydrogen bond acceptors, polarizability, polar surface area, Caco-2 cell model (human epithelial colorectal adenocarcinoma cells used to model the gut–blood barrier), central nervous system activity, human serum albumin binding] were calculated using the QikProp program.<sup>28</sup> These descriptors account for various aspects of drug absorption and distribution such as solubility, membrane permeability, bioavailability in serum, gut–blood barrier permeability, and brain–blood barrier (BBB) permeability (see Supplementary Information).

#### *Quantitative Structure–Activity Relationship (QSAR) model*

Multiple linear regression (MLR) was carried out using the Strike statistical program<sup>28</sup> to search for the best QSAR predictive model. MLR was performed on the 25 medications, represented by their ATS scores, 7 QSAR parameters, and ADE incident rates. The QSAR models were analyzed using leave-1-out cross validation. Model quality (goodness of regression and prediction) was determined by  $R^2$  (coefficient of determination) and  $Q^2$  (cross-validated or predictive  $R^2$ ).

## **Results**

The 25 medications, their corresponding drug classes, receptor-specific/total ATS scores, and ACB/ARS scores, are listed in Table 1. Antihistamines, antipsychotics, and gastrointestinal agents account for a majority of the 25 medications. Receptor-specific and total ATS scores range 0–1 and 0.60–5.00, respectively. Overall, 14 out of the 25 medications have receptor-specific ATS scores of 1.0 for all five muscarinic receptors. The other 11 drugs have variable degrees of receptor inhibitions with total ATS scores ranging 0.60–3.90.



**Figure 2.** Correlations between ATS/ARS/ACB scales to cumulative incidence rate of ataxia. ACB, anticholinergic cognitive burden; ARS, anticholinergic risk scale; ATS, anticholinergic toxicity score.

Figure 2 shows the cumulative incidence rate of ataxia, the most common form of AC-related ADE identified in the retrospective cohort study (Table 2), computed across all 25 medications on an ordinal scale for direct comparison of ATS against previously reported ACB and ARS methods.

The retrospective cohort study included 287,614 exposed and 287,614 unexposed patients. Table 2 shows that mean age was 38 years (median = 39 years, range = 5–84 years); less than half (44%) patient population were men; the mean length of follow up was 33 days (median = 9 days). The exposed cohort had significantly higher level of comorbidities (CCI 0.38 *versus* 0.32,  $p < 0.05$ ) than the unexposed cohort. Ataxia was the most common ADE (7%). Among the 25 medications, promethazine was the most prescribed (received by 36% patients).

Table 3 shows the number of ADEs in the exposed cohort and adjusted for baseline ADEs in the unexposed cohort for each of the 25 medications. The number of ADEs were used to calculate the clinical risks (i.e. cumulative incidence rates) of overall AC-related ADEs and tachycardia.

MLR using ATS and drug bioavailability-related parameters yielded a QSAR model with excellent correlation to overall AC incident rates ( $R^2 = 0.83$ ) and predictive performance [cross validation  $Q^2 = 0.64$ ; Figure 3(a) and Supplementary Information]. Good correlation and predictive

performance ( $R^2 = 0.67/Q^2 = 0.29$ ) were also obtained for an M2 receptor-specific QSAR model and tachycardia, an M2 receptor-specific ADE [Figure 3(b) and Supplementary Information].

## Discussion

### ATS versus other toxicity scales

Previously published AC toxicity scales employed one of two techniques for classifying drugs as mild, moderate, or high AC activity: (1) measurement of serum radio-receptor anticholinergic activity (SAA) or *in vitro* affinity of drug binding to muscarinic receptors, and (2) classification of AC activity by an expert panel of clinicians (i.e. Delphi method). However, SAA only measures peripheral AC activity and may not represent CNS AC effects. Thus, an association between cognitive impairment and SAA has not been consistently demonstrated.<sup>29,30</sup> *In vitro* binding studies have not been reported for many medications and would be expensive to undertake given the large number of commercially available drugs. Finally, expert opinion, although widely employed, is subjective as demonstrated by differences in ranking between specific drugs (Table 1) and the wide variability of drugs selected in current scales. Duran and colleagues have shown considerable variability across current toxicity scales when a comprehensive list of over 120 medications is compared.<sup>19</sup>

Our exploratory work yielded a novel toxicity scoring system that begins to address some of the weaknesses of other published scales, such as: (1) AC toxicity is unlikely to conform to an ordinal scale; (2) different scales evaluated different sets of medications; (3) many medications were not scored consistently across different scales; and (4) off-target drug interactions and muscarinic receptor subtype specificity were not considered. Despite these limitations, attempts to predict AC-related ADEs have shown generally positive associations,<sup>17,30</sup> suggesting that a further improved method may lead to clinical utility.

Figure 3 shows that ATS is better suited for differentiating increasing severity of ADE risks than ACB and ARS. The cumulative AC incidence rates generally rise with increasing ATS scores whereas ACB and ARS deviate from AC incidence trend. Our approach is intrinsically different from all previous reported methods and offers the following advantages: (1) pharmacologically driven by large and diverse bioactivity databases;

**Table 3.** AC-related ADEs and ATS scores by medication.

	Number of exposed patients	Percent of exposed patients	Number of all ADEs <sup>b</sup>	ADE incidence rate (per patient)	Number of tachycardia <sup>b</sup>	Tachycardia incidence rate (per 100 patients)
Promethazine	103,960	36.15	7148	0.07	319	0.31
Chlorpheniramine	42,277	14.70	2268	0.05	42	0.10
Alprazolam <sup>a</sup>	36,969	12.85	5292	0.14	399	1.08
Diazepam <sup>a</sup>	29,615	10.3	2112	0.07	124	0.42
Ranitidine	17,962	6.25	2977	0.17	162	0.90
Brompheniramine	17,238	5.99	1030	0.06	24	0.14
Amitriptyline	10,357	3.60	2706	0.26	204	1.97
Atropine	10,334	3.59	1140	0.11	43	0.42
Dicyclomine	9499	3.30	1252	0.13	48	0.51
Hyoscyamine	8566	2.98	1044	0.12	41	0.48
Diphenhydramine	5956	2.07	481	0.08	16	0.27
Orphenadrine	4316	1.50	308	0.07	15	0.36
Risperidone <sup>a</sup>	2854	0.99	626	0.22	42	1.46
Carbinoxamine	1803	0.63	89	0.05	2	0.10
Fentanyl	1646	0.57	828	0.50	54	3.29
Imipramine	1280	0.45	290	0.23	15	1.16
Loperamide	1078	0.37	190	0.18	11	1.05
Clorazepate <sup>a</sup>	735	0.26	112	0.15	10	1.30
Benztropine	322	0.11	159	0.49	12	3.88
Chlorpromazine <sup>a</sup>	272	0.09	60	0.22	5	1.97
Haloperidol <sup>a</sup>	203	0.07	82	0.40	8	3.81
Trihexyphenidyl	118	0.04	52	0.44	3	2.52
Perphenazine <sup>a</sup>	76	0.03	27	0.36	3	3.91
Thioridazine <sup>a</sup>	24	0.01	7	0.30	1	2.48
Trifluoperazine <sup>a</sup>	19	0.01	14	0.76	1	3.13

<sup>a</sup>Agitation, irritability, and hallucinations were not included as eligible ADEs if a patient had any fills for antipsychotics or benzodiazepines.

<sup>b</sup>Adjusted using baseline ADEs in the unexposed cohort.

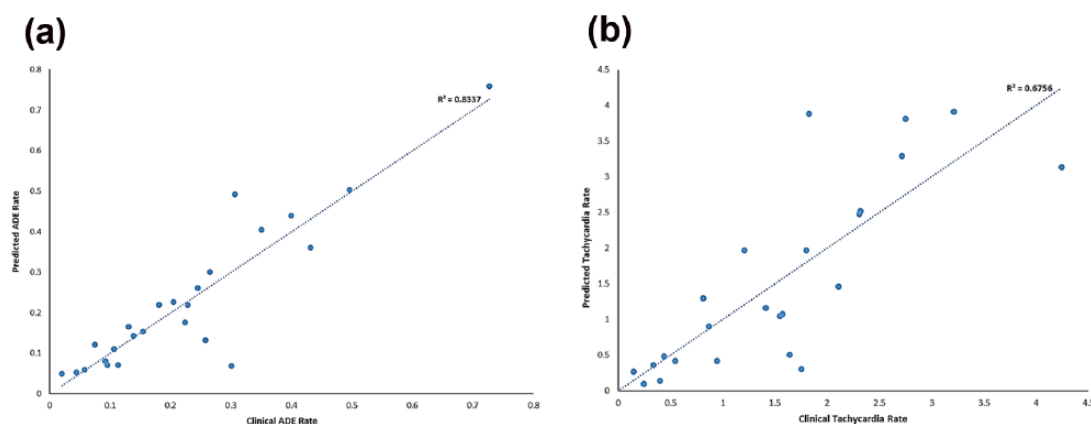
ADE, adverse drug event; ATS, anticholinergic toxicity score.

(2) receptor subtype-based scoring which may provide greater sensitivity; (3) greater resolution on a continuous toxicity scale; and (4) it is objective, systematic, efficient, and scalable to a large number of medications.

### Receptor subtypes

Table 1 demonstrates a strong similarity among many medications that are similarly active across

all five muscarinic subtypes (i.e. similar ATS scores across all receptor subtypes). However, for some drugs such as alprazolam (active only on M4 and M5) and ranitidine (active only on M1 and M2), interactions at specific muscarinic receptors could be clinically important. Our QSAR model using M2-only ATS scores suggests that ATS receptor subtype-specific scores may have a potential utility for assessing receptor subtype-specific ADEs [Figure 3(b) and Supplementary Information].



**Figure 3.** (a) QSAR model for overall ADE risk assessment and prediction ( $R^2 = 0.83$ ,  $Q^2 = 0.64$ ,  $F = 10.0$ ,  $p < .00001$ ); (b) QSAR model for M2 receptor-specific tachycardia risk assessment and prediction ( $R^2 = 0.68$ ,  $Q^2 = 0.29$ ,  $F = 4.2$ ,  $p < .001$ ).

ADE, adverse drug event; QSAR, quantitative structure–activity relationship.

#### ATS-based toxicity predictive model and future work

The strong association between our ATS-based QSAR model and ADE incidence rates provides encouraging hope for the development of a clinically useful toxicity prediction scale [Figure 3(a) and Supplementary Information]. Currently, ATS scores only represent the pharmacodynamic interactions of medications with muscarinic receptors. Drug pharmacokinetic parameters also must be considered to assess AC clinical risks. For example, despite having a maximum total ATS score of 5, the pharmacokinetics of atropine and its low dosage present in the prescription product Lomotil® yielded relatively low ADE incidence rate (i.e. insignificant ADE risks). Adding additional parameters to adjust for dose and pharmacokinetic effects will be important for clinical utility. To test this hypothesis, we used an *in silico* pharmacokinetic program to calculate several key absorption and distribution parameters for the 25 medications. The excellent correlation to overall AC incident rates ( $R^2 = 0.83$ ) and predictive performance (cross validation  $Q^2 = 0.64$ ) demonstrates the importance of combining ATS scores and drug pharmacokinetic parameters for developing a clinically significant predictive model [Figure 3(a) and Supplementary Information]. We also combined the same set of pharmacokinetic parameters with receptor subtype-specific ATS scores to assess ADEs originating from inhibition of specific muscarinic receptor subtypes. As an example, tachycardia is considered primarily related to M2 receptor inhibition. The good correlation and predictive performance of the M2

only QSAR model ( $R^2 = 0.67/Q^2 = 0.29$ ) support that ATS can be potentially used to characterize the receptor subtype specificity of ADEs [Figure 3(b) and Supplementary Information]. Although dosage information was not included in the current study, future work will include dose and parameters to address drug clearance and elimination, etc. Our main goal in this pilot study is to obtain the best overall ADE (CNS and peripheral) model for the general population. The same computational protocol can be followed to build models specifically for subpopulations such as elderly patients (age 65+) or patients with ‘compromised BBB’ if the cohort can be properly defined by age and medical conditions.

#### Study limitations

The current ATS approach, while offering a foundation for objective and systematic AC toxicity evaluation, can be further improved by incorporating the following areas: (1) clinical pharmacokinetic and bioavailability data; (2) dosage and duration of treatment; (3) patient genomic variability in drug metabolism and pharmacodynamics; and (4) perhaps most importantly, investigation of other polypharmacologic drug actions contributing to similar ADEs. Additionally, confounding by indication and under reporting of ADEs in claims data are potentially limiting factors that may lead to inaccurate determination of clinical outcomes. Nevertheless, the ATS scoring approach and ATS-based predictive models highlight opportunities for further improvements while avoiding patient safety



concerns. After further refining the ATS scoring system, clinical outcome determination and validation can be undertaken using more robust randomized controlled clinical studies.

### Conclusions

To our knowledge, our ATS scoring method represents the first application of big data-driven bioinformatics and biomedical informatics aimed at direct translation to patient care. Pilot results from this test-of-concept work demonstrate the potential and feasibility of the ATS approach in improving clinical AC toxicity assessment and that further development and refinements are warranted. Optimistically, ATS may provide a rational path forward for assessing and predicting cumulative AC-related ADEs resulting from concomitant AC medication use. The ATS computational methodology may even be adapted to facilitate rapid rational assessment of other types of drug-induced toxicity.

### Funding

This work is supported in part by ALSAM Foundation Skaggs Scholars Award to D.X., H.A., R.V. and V.C., NIGMS IDeA Mountain West Clinical and Translational Infrastructure Network (CTR-IN) Mini and Pilot Grants (1U54GM104944-02/15-746Q-ISU-MG5-00, 5U54GM104944-03/16-746Q-ISU-PG44-00) to D.X. and V.C., and Idaho State University Faculty Seed Grant to D.X. and V.C.

### Conflict of interest statement

The authors declare that there is no conflict of interest.

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