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A novel machine learning approach to anticholinergic burden quantification

Christopher Fleetwood 1, Mahan Salehi1, Rachel Ward 1, Hulka Mamayusupova1, Agostina Secchi 2, Simon Coulton 3, Ian D. Maidment4, Phyo K Myint 5, Chris Fox 1, Saber Sami 1

1 Norwich Medical School, University of East Anglia, UK; 2 Kent and Medway NHS & Social Care Partners; 3 Centre for Health Services Studies, University of Kent, Canterbury, UK; 4 School of Life and Health Sciences, Aston University, Birmingham, UK; 5 Ageing Clinical & Experimental Research Team, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK;

* Correspondence: s.sami@uea.ac.uk;

Keywords: Anticholinergic; Polypharmacy; Aging; Natural Language Processing; Machine Learning;

Summary

Background

Anticholinergic medications have been associated with accelerated memory and language deterioration with increased risk of Mild Cognitive Impairment (MCI), particularly in older people. Accurate quantification of total anticholinergic burden (ACB) is a critical first step to prevent cognitive decline in the geriatric population. Whilst there are at least 16 different anticholinergic burden scales available, inconsistency exists between these scales due to the methods employed in their development and the different interests and expertise of developers with regard to outcomes. We aimed to develop a universal ACB scoring system using machine learning techniques for a fully automated model accessible through a web-based portal.

Methods

A novel machine learning system was developed using textual samples from published sources describing medications scored on previously established anticholinergic burden scales which were well validated against several health outcomes. Our semi-supervised approach ensures that maximal information from these scales is utilized. The algorithm provides the ability to rapidly classify existing medications and maintain surveillance of new emerging medications. In order to validate the approach, a chemical structure based analysis was performed to explore homogeneity between innate chemical structure and the new ACB scoring system.

Findings

Usage of the newly created International Anticholinergic Burden Scale (IACB) significantly improves the ACB scale accuracy compared to previous scales (AUC 0.91). An analysis of chemical structure found a stronger correlation between the IACB and the underlying chemical structure of medications when compared to 6 currently used scoring systems. To increase accessibility to this newly created scale, a web portal was developed to provide clinicians and patients with accurate information on their current total anticholinergic burden.
Interpretation

Usage of Machine Learning can potentially build upon previous attempts at anticholinergic burden quantification, overcoming language barriers and aligning closely with innate medication structure allowing for a more accurate, up-to-date scoring system.

Funding

UEA impact fund 192008.

Introduction

The quantification of the anticholinergic activity of medications is of increasing interest due to recent understanding that anticholinergic activity significantly contributes to the harms of polypharmacy in the ageing population.\(^1,2\) Polypharmacy in older adults has been associated with an increased risk of falls and co-morbidities, and this association is stronger as the number of anticholinergic medications consumed increases.\(^3\) In more recent years, there have been growing concerns over anticholinergic medications exacerbating mental decline through cognitive impairment,\(^2,4\) where anticholinergics have been associated with accelerated memory and language deficiencies as well as increased risk of Mild Cognitive Impairment (MCI), particularly in individuals with genetic risk factors.\(^5\) Due to the growing number of ageing populations across the world, it is expected that there will be a significant rise in the incidence and prevalence of cognitive impairment over time, resulting in increased medical, social and financial costs. Current dementia treatments are primarily focused on prevention with a limited group of medications available to delay the development of symptoms. Anticholinergic use has been identified as a potentially modifiable risk factor to aid this prevention.\(^3\) Subsequently, numerous anticholinergic drugs are known to be inappropriate medications for older adults.\(^6\) Despite this, anticholinergic use is sharply increasing; in England alone, potent anticholinergic usage in older adults has nearly doubled from 5.7% in 1990-93 to 9.9% in 2008-11.\(^7\) Furthermore, the usage of any anticholinergic medication (medications scoring 1, 2 or 3 on the Anticholinergic Cognitive Burden scale)\(^8\) increased from 49.6% to 64.3% in the same period.\(^7\)

Currently, at least 16 anticholinergic burden related scales have been developed.\(^9\) A number of these scales are based on traditional methods, such as expert consensus, literature reviews and serum anticholinergic activity (SSA) - a radioreceptor assay used to quantify anticholinergic burden by the cumulative effect of medications and their metabolites. Since the production of these scales, the flaws of expert consensus have been raised, the limitations of literature reviews undertaken, and the use of SAA has since been rendered as having questionable use in relation to polypharmacy and anticholinergic burden due to mixed results over its efficacy in terms of adverse outcomes.\(^10\) The number of drugs used in these scales varies from 27-520, and scales are required to be regularly updated or face the risk of becoming out-of-date with reduced utility.\(^9\) Furthermore, homogeneity between the scales remains inconsistent and leads to uncertainty for clinicians when deciding which scale is the most appropriate to use in practice.\(^11,9\)

A separate systematic review and meta-analysis conducted by Graves-Morris et al.\(^11\) found it was not possible to confirm any superior anticholinergic burden measure due to a high risk of bias in the scales examined.\(^11\) This indicates a level of turbidity in the literature concerning optimal selection and reliability of anticholinergic burden scales.

The use of machine learning has been suggested to improve drug safety methods having been used in several studies examining adverse drug reactions.\(^12,13\) Machine learning has long been used in extracting medication information from text. One model was used to extract useful information such as name, dose and indication of medications from patient’s electronic health records.\(^14,15\) Advancing this further, another model has been able to identify adverse effects of medications and its relations to other drug attributes such as dose and route.\(^16\) The success and the applicability of machine learning
in patients’ health records to carry out a specific task from unstructured narrative text validates its use within healthcare. Consequently, we propose a data-driven approach to anticholinergic burden quantification. Using a machine learning algorithm trained on biomedical text, we are able to quantify the anticholinergic burden of medications based on their descriptive textual features found in medical literature. To our knowledge, no other scoring system using machine learning on textual documents for anticholinergic burden quantification currently exists.

We aimed to develop a new anticholinergic burden scale, the International Anticholinergic Cognitive Burden (IACB) scale, using machine learning to combine previous information from seven of the most effective anticholinergic burden scales previously identified by Lozano-Ortega et al. using textual data from 3 medication information sources. This new scale aims to succinctly inform clinicians of the anticholinergic burden of medications and assist in more accurate prescription. We also aimed to develop a web-based system that regularly allows for automatic classification of new medications upon their release to the market, and will be easily accessible to clinicians at time of prescription. Our further aim was to validate the system by examining the correlation between underlying chemical structure and the newly created IACB.

Research in context
Evidence before this study
We established the current state of anticholinergic burden quantification by first exploring published literature via PubMed and Google Scholar up to August 2020, with the search terms "Anticholinergic", "Anticholinergic burden" and "Natural Language Processing". We found a number of reviews exploring the topic and used them as the foundation for the current state of the field. Next, we investigated the application of machine-learning methods to anticholinergic medication descriptions and found that it is yet to be performed.

Added value of this study
This study serves as the first usage of machine-learning methods for an end-to-end system of anticholinergic burden quantification. The IACB normalizes previously conflicting anticholinergic scales into a homogeneous single point of reference whilst improving micro-averaged AUROC by 0.13. An unbiased analysis of the chemical structure of the included medications also found that the IACB aligns closer to the natural clustering. Furthermore, the creation of the online web portal will increase the ease of access to not only the IACB, but information about anticholinergics as a whole.

Implications of all the available evidence
The results of our study suggest that there are avenues for improvement over the currently available anticholinergic burden scale. The IACB also strongly indicates that a number of previously low scoring medications should be subject to re-review due to their potentially misclassified anticholinergic potency.
Methods

The International Anticholinergic Burden scale is based on a robust machine learning algorithm, allowing for inclusion of further processing stages, external data, and further validation stages to be implemented.

Dataset

The initial list of medications included in this study are those collated by Lozano-Ortega et al. In their review, they identified 6 scales from the 16 reviewed as being suitable for database analysis. In addition to the 6 identified in their review, we also included the Clinician-Rated Anticholinergic Scale (CrAS), which met all of our review requirements, however was not included in their final analysis.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic Cognitive Burden Scale (ACB)</td>
<td>Boustani et al.</td>
</tr>
<tr>
<td>Anticholinergic Risk Scale (ARS)</td>
<td>Rudolph et al.</td>
</tr>
<tr>
<td>Anticholinergic Drug Scale (ADS)</td>
<td>Carnahan et al.</td>
</tr>
<tr>
<td>Anticholinergic Burden Classification (ABC)</td>
<td>Ancelin et al.</td>
</tr>
<tr>
<td>Anticholinergic Activity Scale (AAS)</td>
<td>Ehrt et al.</td>
</tr>
<tr>
<td>Anticholinergic Load Scale (ALS)</td>
<td>Sittironnarit et al.</td>
</tr>
<tr>
<td>Clinician-Rated Anticholinergic Scale (CrAS)</td>
<td>Han et al.</td>
</tr>
</tbody>
</table>

Table 1. All 7 included scales in this investigation, from a wide variety of geographic locations and patient populations in order to ensure that the IACB is applicable in a wide variety of clinical settings.
In order to determine the general consensus about each medication, the scores were accumulated and averaged (e.g., Atropine scored 3, 3, 3, - , - , 3 in ACB, ARS, ADS, ABC, AAS, ALS, CrAS (- signifying Atropine not being present in the respective scale) respectively and thus a total score of 15 with an average score of \( \frac{15}{5} = 3 \)). The Anticholinergic Drug Scale\(^{19} \) includes different application methods, such as ophthalmic, topical or inhaled preparations. Due to the textual references being composed of information at a general medication level and containing descriptions of effects for a number of different application methods, we omitted different application methods from the dataset. Upon the removal of different application methods, 654 medications remained, with a score distribution shown in Figure 2.

![Figure 2](image)

**Figure 2.** Number of medications in each score category, with legend colourized to differentiate score. The corresponding scales are detailed in Table 1.

As evidenced by Figure 2, there is a heavy imbalance in the dataset towards medications scored at 0 and 1, with the imbalance originating primarily from the Anticholinergic Drug Scale (ADS)\(^{19} \) and the Anticholinergic Load Scale (ALS).\(^{22} \) In order to alleviate the imbalance, a subset of medications were selected to include in the final review. To obtain this subset, firstly we grouped the medications from score 3 and 4 from the Anticholinergic Activity Scale (AAS) such that all 7 scales spanned the same range. Next, we selected all medications from scores 2 (25) and 3 (37) and a subset of 80 for both scores 0 and 1. The selection process and filtering is detailed in Figure 3.

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Programmatic Access</th>
<th>Author</th>
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</thead>
<tbody>
<tr>
<td>Drugbank.ca</td>
<td>YES</td>
<td>Wishart et al.(^{24} )</td>
</tr>
<tr>
<td>PubChem</td>
<td>YES</td>
<td>Kim et al.(^{25} )</td>
</tr>
<tr>
<td>Wikipedia</td>
<td>YES</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Collation of the different data sources used in the investigation.

To maximise accessibility to the data and ensure our findings are reproducible, we obtained data from publicly available sources. We collected textual descriptions from the data sources shown in Table 2. By selecting from a number of different sources, we ensure that the data is varied and whilst being invariant to factors such as location and data collection protocols.
Textual Processing

Once the textual sources had been collected and the subset selected, we employed the usage of an industry standard biomedical text preprocessor, SciSpacy. SciSpacy is a machine learning based text preprocessor designed for processing biomedical, scientific or clinical text. This was particularly suited to our corpus and was selected as the most appropriate technology. A detailed description of SciSpacy has been previously documented and should be referred to for more detail. The large variant of the preprocessor was chosen in order to maximise the available vocabulary, which is diverse in our corpus due to the variety of medications included. Upon obtaining the processed text from each of the data sources, the text was collated into a single descriptive document for each of the medications and proceeded to the vectorization stage. This study employs the usage of term frequency-inverse document frequency vectorization, a process that allows for a numerical representation of each medications’ compiled document to be obtained.
Utilization of existing information

Previous scales included in this study provide us with interesting insights into the general consensus on a medications anticholinergic effects in the literature. In order to make maximal use of the available information, we introduce the concept of “Consensus Medications”, medications which have a unanimous score consensus across 2 or more of the included scoring systems. We treat these “Consensus Medications” or CMs as labelled samples in this investigation due to the agreement on the medications anticholinergic effect despite different practitioners, patient populations and methodologies. To utilize these CMs, we make use of methods suited to a semi-supervised approach, allowing the CMs to act as labelled samples, and treating medications for which there are discrepancies in scoring between scales as unlabelled samples. For dimensionality reduction to allow for reasonable clustering computation time, we employed Semi-Supervised Linear Discriminant Analysis. For clustering, we employed COP-KMeans, a clustering algorithm that allows for the specification of data points that must be clustered together and data points that cannot be clustered together.

Cluster Validity Analysis

Whilst 6/7 of the scales included in this study use a 0-3 (4 point) scaling approach, in order to evaluate the optimal scale range for the data collected, a cluster validity analysis was performed. In addition, one of the scales, the Anticholinergic Activity Scale, used a 0-4 point (5 point) scale, meaning that there is some confusion in the current literature over the optimal approach. To determine the optimal number of clusters, we performed a cluster validity analysis using Cluster Validity Indices (CVIs). In their extensive review of available CVIs, Arbelaitz et al. found that Silhouette Coefficient, Normalized Davies-Bouldin and the Calinski-Harabasz Index consistently outperformed the other CVIs tested. Due to the lack of widely reviewed implementations of Normalized Davies-Bouldin, we opted for the usage of the standard Davies-Bouldin Index. We ran the clustering algorithm for each number of clusters and compared the CVIs in order to choose the optimal number of clusters.

Chemical Validation

To obtain quantitative metrics of the scales performance, a chemical structure analysis was performed to determine the correlation between the scoring systems and the innate chemical structure of the medications. To achieve this, molecular structures openly available from Drugbank were used to compute Extended Connectivity Fingerprints (Morgan Fingerprints) for each of the molecules, with the connectivity fingerprints enabling medication to medication comparison. We repeated this for each of the individual scales so as to perform a pairwise comparison, using the overlapping subset of medications available in both the IACB and the scale in question. We omitted the ABC as it did not score enough medications to construct the desired clusters. Next, we computed pairwise Dice Similarity coefficients in order to quantify how similar 2 different molecules are. This then allowed for us to cluster together medications based on their similarity coefficients, using Hierarchical Ward Clustering, an agglomerative clustering technique allowing groups of samples to collect together with each iteration. The core hypothesis behind this validation method being that drugs with a similar structure should exhibit similar central and peripheral anticholinergic effects due to medications of a similar structure having similar affinity to the muscarinic receptors. We clustered the medications across a range of clustering values. This is due to the many different medication families (e.g antipsychotics, anticonvulsants, bladder muscarinics) capable of causing similar anticholinergic effects within each scoring category. We selected a range of values from 10 to 25 in an attempt to capture these families. Once the hierarchical clustering had been performed, we computed the mean score value for each of the clusters. Using this mean, we computed the mean absolute error between the scoring system in question and the mean score value, with a better scoring system demonstrating minimal variation between it’s assigned labels and the mean score. In order to have a direct comparison, we scaled the IACB’s 5 point scale into the range of the scale that it was being compared against. Analysing the
correlation between the scores assigned and the mean score allows for the identification of the labelling system more closely correlated with underlying chemical structure.

Role of the funding source

UEA Impact fund had no role in the study design, data collection, analysis or interpretation. All authors had full access to all the data used in the study and had final responsibility for the decision to submit for publication.

Results

Classification

In order to compare the different labelling systems performance, we used trained a linear model with stochastic gradient descent and performed 10-fold cross validation to obtain a strong understanding of the classifiers performance. We then computed the AUROC for all classes when the classifier is trained using the IACB or the average of 7 scales as the ground truth. 95% Confidence intervals for the AUC were computed with the DeLong method. Figure 4 clearly demonstrates the improvement in classification result using the IACB scale when compared to the average of the 7 scales. Training a classifier also provides the advantage of being able to classify previously unseen medications without the need to perform clustering. More information regarding classifier hyperparameters and tuning is available in the Supplementary Material.

![Figure 4A] Receiver operating characteristic curve IACB

![Figure 4B] Receiver operating characteristic curve AVG7

Figure 4. Receiver operating characteristic curves

Figure 4A) Receiver operating characteristic curves for the 5 point (0-4) classification averaged across 10 fold stratified cross validation using the IACB as the ground truth. Figure 4B) Receiver operating characteristic curves for the 4 point (0-3) classification averaged across 10 fold stratified cross validation using the AVG7 as the ground truth. 95% CI shown in brackets. AUC = area under the curve.

Figure 4B) demonstrates that the average of 7 scales provides good classification performance for medications of high anticholinergic potency, but struggles to classify scores 1 and 2. In contrast, the IACB performs well across 2, 3 and 4. The IACB scale highlighted outliers which scored high, potentially very strong anticholinergic medications, previously assigned lower ACB scores in the 7 prior scales. Particular candidates of interest are Haloperidol and Prochlorperazine, being assigned high scores despite low scores in other scales. These candidates should be subject to re-review of their anticholinergic potency.
Chemical Validation

The IACB labelling system matches closer to the innate chemical structure of the medications despite having no prior knowledge of chemical structure. Interestingly, members in the same cluster often belong to the same medication groups (i.e. antidepressants or antipsychotics) and tend to have the same score assigned independently by the IACB. This is particularly true for clusters which contained drugs with IACB scores 3 and 4, thus showing agreement between the Extended Connectivity Fingerprints and textual methods. Our analysis found that medications assigned a higher IACB score typically featured a benzene ring, or secondary/tertiary amine groups. Our observations also show that Nitrogen substitutions within benzene rings and the addition of "aldehyde oxygen= double bonded oxygen" to the benzene ring can reduce the cholinergic effect. Tri-cyclic structure of some medications such as antidepressants (amitriptyline, imipramine) and antipsychotics (doxepin, chlorpromazine) and di-cyclic structure of antihistamines (chlorpheniramine, doxylamine) and bladder antimuscarinics (tolterodine, oxybutynin) were shown to be related to these medications’ high anticholinergic potency and could be the subject of further investigation. In contrast, medications with longer chains show less anticholinergic potency; such as cimetidine. Unlike human observation of chemical structures of molecules, Extended Connectivity Fingerprints analyses the relationship each atom has to a neighbouring atom, assigning unique codes to a structure. In this manner, the algorithm is more systematic and precise.

As drugs with similar chemical structure should exhibit similar central and peripheral anticholinergic effects, we should expect that when medications are clustered together based on chemical similarity, that there is minimal variation in scores in the same cluster. Mean absolute error values for each pairwise normalized comparison are demonstrated in Figure 5.

![Figure 5](image)

**Figure 5.** Pairwise comparison of mean absolute error averaged across 10-25 clusters between the IACB and 6 other scales. Mean absolute error is bounded between 0·0 and ∞, with lower being better. The groups having significant difference between them are denoted by * (\(^*\) refers to \(p \leq 0.05\), ** refers to \(p \leq 0.005\), and *** refers to \(p \leq 0.0005\)).

Discussion

Our new system proposes a novel and agile approach in scoring anticholinergic burden of medications. Using textual information, we were able to rapidly assign ACB scores for previously unseen medications providing significant improvement over current widespread scoring systems. The
use of machine learning techniques ensures our database is constantly evolving and new medications can be scored with ease via a web-based scoring system, allowing for universal access. Newly licensed medications with adequate textual descriptions can be quickly added after release and be scored using our approach, provided they have a minimum of 2500 words of description for the system to assess a drug accurately. One suggested approach to deal with new samples with sparse medical literature is to perform chemical validation through comparison of its chemical structure to the existing clustered medications and assigned a "prospective chemical score", similar to the score of the members of the cluster it belongs to.

Our study improves upon previous work in several ways. Firstly, we remove the implications of variations in expert opinion from the data and provide qualitative and quantitative metrics for determining an accurate picture of a medications anticholinergic impact. Secondly, we draw data from all currently available high-quality anticholinergic scales and normalize their scoring, factoring both their provided information and the textual information. The IACB also provides a spotlight on certain medications with which the system strongly disagrees with previous consensus. There have been numerous attempts at accurately quantifying total anticholinergic burden, with each using different metrics in order to measure the anticholinergic effects of medications. There are at least 16 anticholinergic burden scales reported in the literature. The Anticholinergic Burden Classification (ABC) is the oldest of the scales we have used in our comparison and included 372 elderly participants. Using a combination of both serum radioreceptor assay and average estimated effects of drugs, they found continuous users of anticholinergic medications to be at a significantly higher risk of developing mild cognitive impairment. The Anticholinergic Cognitive Burden Scale (ACB) was a literature review which showed acute and possibly chronic cognitive impairment in the elderly population who take anticholinergics. This three-tiered scoring system considered serum radioreceptor anticholinergic assay, drug affinity to muscarinic receptors using in vitro measurements and an expert list of medications. ACB remains the most validated tool based on citation analysis. The Anticholinergic Risk Scale (ARS) utilised medical records of 117 elderly patients and showed a statistically significant association between ARS and adverse effects of anticholinergic medications. They also developed a three-tiered scoring system based on expert opinion and information available in the literature. The Clinician-Rated Anticholinergic Scale (CrAS) was another three-tiered scoring system based on expert opinion which was shown to be statistically significantly associated with short-term memory and executive function. The Anticholinergic Drug Scale (ADS) carried out multiple linear regressions on serum anticholinergic activity (SAA) and a four-tiered scale whilst also adjusting for the dose. The Anticholinergic Activity Scale (AAS) is a five-tiered scale combining both in vivo radioreceptor assay and available information in the literature. They found a statistically significant association between a decline in cognition and anticholinergic use in a group of 235 elderly Parkinson's disease patients. The Anticholinergic Load Scale (ALS) is another scale using both SAA and expert opinion which showed a statistically significant association with mental function decline.

Each individual scale has been developed using a different approach; these are labour intensive and time consuming, requiring expert opinion and manual search of the literature. This static approach means that scales must be updated or risk becoming out-dated as more literature and medications become available.

The algorithm produces 20 outliers (medications with a score difference greater than +/− 1 on any previous scale) from the 222 medications scored. Of particular interest of these outliers are the 2nd generation antihistamines (Levocetirizine, Cetirizine, Desloratadine, Loratadine and Fexofenadine). All 5 of these medications have been classified as scoring 4 on the IACB by the algorithm, despite previously scoring of a maximum of 2 (on 0-3 scales). Whilst this may be too severe, evidence has shown that second-generation antihistamines can affect movement control and cause other anticholinergic side effects. We believe that with more diverse datasets and enhanced document vectorization techniques our semi-supervised approach could further improve.
There are a number of avenues that could be utilized in order to further enhance the performance and validity of the IACB. Due to the decreases in cost for high performance matrix computation, the usage of deep learning in natural language has enabled impressive capabilities in domain specific lexical understanding. However, this approach is currently unsuited for this task due to the extremely restricted dataset size, of which deep learning methods particularly struggle with. It is due to this limited dataset size that we also employed cross validation, in contrast to an out of sample holdout dataset which would be preferred if not for the data sparsity. There are a number of factors that we were unable to factor into the algorithm that may contribute to improved patient outcomes, particularly the inclusion of different scores for the same medications based on dosage. Factoring average daily dose or cumulative dose would enable more accurate quantification at prescription time. Another further avenue worthy of pursuit is the inclusion of subject specific factors such as age, gender and other known covariates. This would allow for the construction of a "personalized” anticholinergic burden calculation leading to improved patient outcomes.

In summary, our results suggest that machine learning based systems could be developed to more accurately quantify anticholinergic burden and improve patient outcomes. Further work should be done to accumulate more high-quality data in order to further improve scoring. Inclusion of factors such as dosage and utilization of information about medication combinations could lead to a personalized anticholinergic burden calculation.

**Author Contributions:** CIF & SS designed the algorithm. All authors were involved in writing and revising the work to ensure important intellectual content, or in the final approval of the version submitted for publication.

**Funding:** UEA impact fund 192008.

**Conflicts of Interest:** These author declare no conflict of interest.

**Data Sharing:** All data used in this investigation is part of the public domain and the protocols provided in this paper can be used to replicated the dataset.


Figure 1: The International Anticholinergic Burden scale is based on a robust machine learning algorithm, allowing for inclusion of further processing stages, external data, and further validation stages to be implemented.

Figure 2: Number of medications in each score category, with legend colourized to differentiate score.
Figure 3: Flowchart of the data collection

PubMed Exploratory Search

699 unique medications across 6 suitable scales identified

Addition of Clinician Rated Anticholinergic Scale increasing medication count to 702

179 medication entries excluded due to insufficient data.

Development dataset containing 523 medications

Clustering dataset containing 222 medications

86 medication entries excluded due to variations in application method (e.g. Ophthalmic, Topical, Nasal) resulting in 616 entries.
A) Receiver operator characteristic curve IACB

B) Receiver operator characteristic curve AVG7

Figure 4: Receiver operating characteristic curves
Figure 4A) Receiver operating characteristic curves for the 5 point (0-4) classification averaged across 10 fold stratified cross validation using the IACB as the ground truth. Figure 4B) Receiver operating characteristic curves for the 4 point (0-3) classification averaged across 10 fold stratified cross validation using the AVG7 as the ground truth. 95% CI shown in brackets. AUC = area under the curve.

Figure 5: Pairwise comparison of mean absolute error averaged across 10-25 clusters between the IACB and 6 other scales. Mean absolute error is bounded between 0.0 and infinity, with lower being better. The groups having significant difference between them are denoted by * (* refers to $p \leq 0.05$, ** refers to $p \leq 0.005$, and *** refers to $p \leq 0.0005$).
A novel machine learning approach to anticholinergic burden quantification - Supplementary

Christopher Fleetwood, Mahan Salehi, Rachel Ward, Hulkar Mamayusupova, Agostina Secchi, Simon Coulton, Ian D. Maidment, Phyo K Myint, Chris Fox, Saber Sami

1 Norwich Medical School, University of East Anglia, UK; 2 Kent and Medway NHS & Social Care Partners; 3 Centre for Health Services Studies, University of Kent, Canterbury, UK; 4 School of Life and Health Sciences, Aston University, Birmingham, UK; 5 Ageing Clinical & Experimental Research Team, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK;

* Correspondence: s.sami@uea.ac.uk;

Keywords: Anticholinergic; Polypharmacy; Aging;

Additional dataset information

The dataset consists of 3 different independent data sources. All 3 data sources were kept up to date up to the 24th January 2021. In order to ensure that the algorithm generalizes to data that could be provided by patients and clinicians in the future, we endeavoured to gather information from different types of sources. The 3 selected are detailed in Table 1.

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<thead>
<tr>
<th>Data Source</th>
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<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Wishart et al. 1</td>
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<td>PubChem</td>
<td>YES</td>
<td>Kim et al. 2</td>
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<td>Wikipedia</td>
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</tbody>
</table>

Table 1. Collation of the different data sources used in the investigation.

For all data sources, programmatic access is provided. DrugBank provides a full XML representation of their database and this was parsed using a custom XML parser in Python. The following fields were extracted from each medications entry to make up the Drugbank medication document:

- Description
- Indication
- Pharmacodynamics
- Mechanism of Action

PubChem provides programmatic access via 2 REST APIs. Due to our requirements for textual information, we opted to use the PUG VIEW API in order to extract the required data. To interface with the API using Python we used a convenient wrapper, PubChemPy to make requests. From the API we extracted only the most relevant information with the fields being listed below.

- Summary
- Livertox Summary
- Pharmacology
- FDA Pharmacological Classification
Wikipedia provides programmatic access via the WikiMedia API. To ensure the data contained only relevant information, we removed the following sections across all queried pages:

- History
- Society and culture
- Names
- Crime
- See also
- References
- External links
- Further reading
- Brand names
- Generic names
- Synthesis
- Trade names
- Regulatory status

Additional Algorithm Details

Each text source was processed through SciSpacy individually and then concatenated to form a single document for each medication. Once the text was processed, we removed any samples with less than 2500 words in order to provide the algorithm sufficient data to create a representative vector.

Next we used TFIDF vectorization in order to vectorize these newly created documents. We employed the use of SciKit Learn's TfidfVectorizer with the following hyperparameters:

- Minimum Document Frequency: 7
- Maximum Document Frequency: 0.7
- Ngram Range: (1,2)
- SMARTIRS: LTC

Classification

In order to determine the optimal classifier, we tested 5 commonly used classifiers on both labelling sets with the following hyperparameters:

- Logistic Regression: 10 C values between $10^{-4}$ and $10^4$ evaluated via Grid Search
- Stochastic Gradient Descent (SGD) Classifier: Normalized 0-1, Huber loss, Iterations: 10000
- Naïve Bayes: 8 α values between $10^{-4}$ and $10^3$
- Complement Naïve Bayes: 8 α values between $10^{-4}$ and $10^3$
- Ridge Classifier: 3 α values between $10^{-1}$ and $10^1$

Dimensionality Reduction

In very high-dimensional spaces, Euclidean distances become inflated and therefore computationally intensive to compute. In order to reduce the number of dimensions of the data, we opted to use Semi Supervised Linear Discriminant Analysis (SDA).\(^3\) showed that SDA outperforms Principal Component Analysis, another popular method of dimensionality reduction. This method allowed us to utilize the information provided by the prior scoring systems, by treating medications with unanimous score assignment as labelled samples whilst still making use of the structural information provided by the unlabelled samples. We used SDA with the following hyperparameters:

- NeighborMode = KNN
- $k = 2$
- WeightMode = Binary
- ReguBeta = 0.1
- ReguAlpha = 0.1

These hyperparameters were chosen as\(^3\) found they achieved maximal performance in their investigations.
Table 2. Comparing the classification results for both the average of the 7 previous scales and the IACB.

<table>
<thead>
<tr>
<th>Metrics</th>
<th>Diagnosis</th>
<th>Classifier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LR</td>
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<tr>
<td>Accuracy</td>
<td>AVG. 7</td>
<td>0.64</td>
</tr>
<tr>
<td></td>
<td>IACB</td>
<td>0.87</td>
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<tr>
<td>p-value</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>AVG. 7</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>IACB</td>
<td>0.90</td>
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<tr>
<td>p-value</td>
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<td>0.0002</td>
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<tr>
<td>Specificity</td>
<td>AVG. 7</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>IACB</td>
<td>0.96</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>F1-score</td>
<td>AVG. 7</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>IACB</td>
<td>0.88</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Selecting $n$ Clusters

When using K-Means or any of its derivatives, typically the hardest part is the selection of the optimal value of $n$ for the clusters. In order to do this, we used a number of different cluster validity indices as detailed in the main paper, testing the outcomes across a 3, 4 and 5 point scale.

Figure 1. This figure shows the normalized values of each cluster validity index, demonstrating the reasoning behind our selection of a 5 point scale when compared to a 3 or 4 point.

Clustering Algorithm

In order to further utilize the information available from medications with unanimous consensus, we chose to employ the use of COP-KMeans. COP-KMeans allows for known samples to be forced together into the same cluster, allowing medications that have confident score assignment to be used as the centroids of the desired clusters. KMeans is an inherently random algorithm, due to the random
assignment of cluster centers during initialization. We employed the usage of the kmeans++ algorithm\textsuperscript{5} in order to improve the speed of convergence. To avoid the randomness in the clustering outcome, we followed the recommended strategies from\textsuperscript{6}, running the K-Means for 100 repetitions and taking the labels for which the sum of squared errors was minimized. This avoids a lack of reproducability introduced by the randomness of the K-Means algorithm, and improves the clustering results.

**Chemical Validation**

By chemically validating our scoring system, we aimed to provide some quantitative metrics to the performance of our scale, based on the innate chemical structure of the medications included. First, we used the provided .sdf file from DrugBank which catalogs the molecular representation of medications in their database. Next, we utilized RdKit to parse these molecular representations and compute Morgan Fingerprints. From these we then computed pairwise Dice Similarity coefficients. This allowed us to convert Similarity into a distance metric (i.e. 0 distance would be 1 similarity). From this, we then performed Agglomerative Hierarchical Clustering using Ward’s minimum variance method. We then used Scipy’s fcluster to flatten the clusters and we selected a range of values from 10 to 25. The reasoning behind not using 5 clusters as the criteria is due to the varied chemical families within each score in both the prior 7 scales and the IACB. Figure 2 demonstrates the results of the clustering.
Figure 2. Dendrogram constructed with the different colours demonstrating the potency of anticholinergic effect. The figure demonstrates the strong correlation between the underlying chemical structure of the medications and the labelling performed by the algorithm, despite the algorithm having no direct chemical structure information provided.

Once we had computed the clustering, we then attempted to validate the scoring systems using the chemical structure. We took the overlapping subset of medications between the IACB and each other scale (ABC was omitted due to scoring too few candidates to perform accurate clustering). The mean absolute error was chosen in order to penalize predictions further from their desired result. In order to provide a fair comparison, we normalized the IACB into the same scoring range as the scale to which it was being compared. This was done by modelling the IACB as a univariate variable and rescaling it to the desired range using the following formula:

\[
\frac{\max_{\text{new}} - \min_{\text{new}}}{\max_{\text{old}} - \min_{\text{old}}} \cdot (v - \max_{\text{old}}) + \max_{\text{new}}
\]
**Topic Modelling**

A further validation method identified as suitable for this investigation is Topic Modelling. Topic modelling allows for the identification of underlying themes in a corpus of documents. This enables the identification of key themes in the collection of documents pertaining to each score cluster. By performing Latent Dirichlet Allocation, underlying topics present in each of the clusters could be identified. Comparison of these topics with previous assumptions to known strong anticholinergic antagonists allows for further validation of the algorithms understanding. Table 3 shows the stratification of different medication classes based on the topics extracted for the documents of the medications in each score category. The results of these keywords matches with previously held beliefs about which classes of medications belong in different score categories.

<table>
<thead>
<tr>
<th>Score 0</th>
<th>Score 1</th>
<th>Keywords Extracted</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>Drug</td>
<td>Pain</td>
<td>Valproate</td>
<td>Antidepressant</td>
<td></td>
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<tr>
<td>Patient</td>
<td>Treatment</td>
<td>Diazepam</td>
<td>Seizure</td>
<td>TCAs</td>
<td></td>
</tr>
<tr>
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<td>Receptor</td>
<td>Withdrawl</td>
<td>Risk</td>
<td>Serotonin</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Form</td>
<td>Glucocorticoid</td>
<td>Antagonist</td>
<td>Antihistamine</td>
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</tr>
<tr>
<td>Blood</td>
<td>Blood</td>
<td>Corticosteroid</td>
<td>Antipsychotic</td>
<td>Allergic</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. The most salient terms for each of the topics extracted from the clusters of literature in each score.

**Web Portal**

As stated in the main paper, we have constructed a web portal to increase accessibility to the IACB, which can be found here: https://iact-app.herokuapp.com/

<table>
<thead>
<tr>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
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<td>sulfasalazine</td>
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<td>triazolam</td>
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</tr>
<tr>
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<td>oxybutynin</td>
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<td></td>
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</tr>
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</table>

This preprint research paper has not been peer reviewed. Electronic copy available at: https://ssrn.com/abstract=3777231
<table>
<thead>
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<th>Brand Name</th>
<th>Generic Name</th>
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<td>dextrose</td>
<td>dextrose</td>
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</tr>
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</table>
etodolac
intestinal flora
vardenafil
trandolapril
reboxetine
pyridostigmine
bimatoprost
zafirlukast
herb
sterculia
cascara sagrada
pirbuterol
ginseng
filgrastim
telmisartan
pioglitazone
doxazosin

Table 4. Table detailing the medications in each scoring category of the IACB