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A review of published anticholinergic scales and measures and their applicability in database analyses

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ABSTRACT

Background/objectives: Available metrics for characterizing cumulative anticholinergic exposure over time may not be well suited for use across all US data sources. In this review, the properties of existing anticholinergic scales and measures were evaluated to determine their suitability for implementation in observational studies relying on administrative data.

Methods: A targeted literature review was conducted to identify available anticholinergic scales and measures. Suitability of the identified scales and measures for quantification of anticholinergic exposure was evaluated based on pre-defined criteria. Agreement between selected scales was characterized by the percentage overlap of included drugs and inter-scale Spearman's correlation of scores.

Results: Sixteen scales were identified; six were relevant and suitable for the quantification of anticholinergic exposure. When implemented on administrative data the Anticholinergic Drug Scale and Anticholinergic Cognitive Burden scale demonstrated the most agreement, with an inter-scale correlation coefficient of 0.82. Scale performance varied by outcome of interest, and underlying disease profile of the population of interest. Variability across the two measures ("average daily dose" and "cumulative dose") was observed, with neither considering both dose and anticholinergic potency in score calculations.

Conclusions: Accurate quantification of anticholinergic burden is important in assessing relative risks versus benefits of prescribing anticholinergic medications. In this review, the Anticholinergic Drug Scale and the Anticholinergic Cognitive Burden scale and the average daily dose and cumulative dose measures, were determined to be well suited for the quantification of anticholinergic exposure, particularly in the context of administrative data analyses; however, methods to characterize anticholinergic burden through consideration of both anticholinergic dose and potency are needed.

1. Introduction

Population aging is a global phenomenon, with the impact of an aging population on healthcare resource use most significant in high income countries (United Nations Department of Economic & Social Affairs, 2015). This is largely due to medical advances, coupled with the ability to diagnose diseases earlier and extend the lives of people with chronic conditions (Christensen, Doblhammer, & Rau, 2009). As medical management of individuals with one or more chronic diseases typically involves the use of pharmacotherapy, it is not unexpected that prescription drug use and polypharmacy have significantly increased over recent years (Kantor, Rehm, & Haas, 2015). Based on a recent cycle of data available from the United States (US) National Health and Nutrition Examination Survey (National Center for Health Statistics (NCHS) (2005), 90% of persons aged 65 years or older are taking one or more prescription medications, and 39% are taking five or more (Kantor et al., 2015).

Older adults with multiple comorbidities are increasingly likely to be prescribed medications with anticholinergic properties (Ruxton, Woodman, & Mangoni, 2015; Salahudeen, Duffull, & Nishtala, 2015), such medications are frequently prescribed to manage conditions including asthma, chronic obstructive pulmonary disease, depression,

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psychosis, Parkinson's disease, allergies and overactive bladder. These drugs are associated with numerous side-effects; indeed, a longitudinal study of patients aged 65 years and older reported baseline use of medications with possible anticholinergic activity in 47% of the population (Fox, Richardson, & Maidment, 2011), while another found that anticholinergic medications were prescribed to approximately 60% of patients aged 75 years and older with dementia (Mate, Kerr, & Pond, 2015). Anticholinergic medications block acetylcholine binding to neuronal cholinergic receptors in the central and peripheral nervous systems (Purves, Augustine, & Fitzpatrick, 2001). This inhibits activation of muscle including that in autonomic effector organs such as the heart, smooth muscle of the gut and exocrine glands (Purves et al., 2001). Although many medications are used specifically for their anticholinergic properties, others have anticholinergic activity that is unrelated to their primary mode of action. As such, they may have non-specific anticholinergic effects that can be associated with unintended side-effects including dry mouth, blurred vision, dizziness and, more rarely, poor psychomotor outcomes (Salahudeen, Duffull et al., 2015; Villalba-Moreno, Alfaro-Lara, & Pérez-Guerrero, 2016). The accumulation of higher levels of exposure due to one or more anticholinergic medications, and the attendant increased risk of medication-related adverse effects, is termed *anticholinergic burden* (Boustani, Campbell, & Munger, 2008).

Given the associations between anticholinergic exposure and adverse clinical outcomes, accurate quantification of anticholinergic burden is valuable in assessing relative risks versus benefits of prescribing anticholinergic medications. Various clinical *scales*, designed to identify anticholinergic exposure to medications at a given point in time, and *measures,* designed to assess anticholinergic exposure longitudinally, have been developed. Scales categorize anticholinergic medications into groups based on their level of anticholinergic potency; this categorization may vary across scales, as some have been validated to capture different elements of anticholinergic activity and drug characteristics. Summary scores are then estimated from the scores assigned to each anticholinergic drug taken by the patient on a given day, with some scales also accounting for dose. High levels of anticholinergic burden, quantified through the use of such scales and measures, have been linked to an increased risk and severity of drug-related adverse effects, including lower physical functioning, higher risk of falls, higher risk of cognitive decline and higher all-cause mortality (Salahudeen, Duffull et al., 2015; Villalba-Moreno et al., 2016). However, the properties of each scale are dependent on the study population and purpose for which they were first created and whether they best assess central versus peripheral anticholinergic effects (Boustani et al., 2008b), as such, there is no ideal scale or measure which is suitable for clinicians and researchers in all circumstances.

While several systematic reviews have been conducted summarizing the different anticholinergic scales and measures currently available (Naples, Marcum, & Perera, 2015; Ruxton et al., 2015; Salahudeen, Duffull et al., 2015; Villalba-Moreno et al., 2016; Welsh, van der Wardt, & Ojo, 2018; Salahudeen, Hilmer, & Nishtala, 2015; Mayer, Meid, & Saum, 2017), to our knowledge, scales and measures have not been critically assessed and compared with the specific purpose of determining their suitability for application in retrospective observational studies using administrative databases. Such databases can be a rich data source for characterizing medication use over time and have the potential to describe anticholinergic exposure longitudinally for large populations. Moreover, retrospective studies that leverage administrative data benefit from a less expensive and time-consuming design compared to observational studies that rely on prospectively collected data. In the present study we evaluated the properties of existing anticholinergic scales and measures for the purposes of determining which are appropriate for implementation in observational studies focusing on patient populations from the US, with a particular focus on administrative database analyses.

2. Materials and methods

2.1. Targeted literature review process

A targeted literature search for publications describing anticholinergic scales and measures was conducted by searching Medline and EMBASE databases as well as studies known to the authors, to identify systematic reviews and analyses quantifying anticholinergic burden (Supplementary Table S1). A comprehensive list of anticholinergic burden scales and measures was compiled for further consideration.

2.2. Suitability of scales and measures for implementation in retrospective database analyses

2.2.1. Preliminary review of anticholinergic scales

Given the large number of available scales to assess anticholinergic burden a preliminary assessment of all anticholinergic scales was conducted. For a scale to be considered in the full review, it was required to have sufficient data provided by authors to allow calculation of summary scores, some grading of anticholinergic potency (i.e. a scale, not a list) and inclusion of high potency medications (as per Duran, Azermai, and Vander Stichele (2013); Supplementary Table S2). While prescribed dose is often not explicitly included in administrative healthcare databases, drug identification numbers normally include details of product strength and can thus be combined with days dispensed to extrapolate daily dose.

Based on these properties, a final list of scales eligible to proceed to full review was compiled.

2.2.2. Full review of anticholinergic scales

Key properties of each scale were summarized, including whether a summary score could be derived that would allow for the quantification of anticholinergic exposure and the population in which the scale was developed. Anticholinergic scales selected for review were evaluated against the following pre-defined criteria; method of development; country of development; year developed; population in which the scale was validated; population excluded from the analysis; optimal target populations; clinical settings in which the scale has been applied; method by which the scale was designed to be administered; ranking mechanism for anticholinergic medication; derivation of summary score; potential ceiling effects/threshold; percentage of prescription medications considered (examined as scales with a high proportion of over-the-counter medications are unlikely to be suitable for use in administrative datasets); number of most common medications considered (as per Salahudeen, Hilmer et al. (2015); and percentage of high potency medications considered Duran et al. (2013). Because of the focus of this review was specifically related to US data sources, the percentage of medications considered that are available in the US was also included in scale evaluation.

Agreement between selected scales was characterized by percentage overlap of included drugs, which represents the proportion of medications given a score by both scales, and inter-scale Spearman's correlation of scores, for which correlations were computed on the scoring agreement within complete observations; i.e., medications for which both scales reported the same score.

2.2.3. Full review of anticholinergic measures

Characteristics assessed for measures included: disease context for which measure was developed; consideration of anticholinergic potency of medications; consideration of medication dose; whether development was based on a specific anticholinergic scale; capability for use with all anticholinergic scales; mathematical properties (e.g., average vs summated score; score boundaries); definition of exposure period; and considerations for categorization of resulting scores.

3. Results

3.1. Anticholinergic scales

Sixteen scales were identified in the preliminary literature review (Supplementary Table S2). Substantial variations were observed among the scales, including the number and type of anticholinergic medications included as well as in anticholinergic potency scores. Ten scales were excluded in the preliminary review phase: eight provided insufficient information to calculate a summary score, two did not consider anticholinergic potency, one provided a list of medications, but with no assigned scores, and one was considered no longer current, with some scales excluded for lacking multiple key characteristics (Supplementary Table S2). The remaining six scales met all criteria and thus proceeded to full review: Anticholinergic Activity Scale (AAS) (Ehrt, Broich, & Larsen, 2010); Anticholinergic Burden Classification (ABC) scale (Ancelin, Artero, & Portet, 2006); Anticholinergic Cognitive Burden (ACB) scale (Boustani et al., 2008b); Anticholinergic Drug Scale (ADS) (Carnahan, Lund, & Perry, 2006); Anticholinergic Loading Scale (ALS) (Sittironnarit, Ames, & Bush, 2011); and the Anticholinergic Risk Scale (ARS) (Rudolph, Salow, & Angelini, 2008).

All scales use an additive approach to estimate daily anticholinergic exposure by adding the scores associated with the anticholinergic drugs being taken, such that individual anticholinergic load may be calculated at any given time. Only the ADS and ARS consider dose in their estimation, with score adjustments made based on an individual's total daily dose received relative to the maximum recommended dose. The target population for all but one of the scales is older adults, the exception being the AAS which targets patients with Parkinson's disease. The association of anticholinergic burden with cognitive function has been investigated with all six scales (Villalba-Moreno et al., 2016). In addition, both the ADS and ARS have been used for investigating associations with specific adverse events (Salahudeen, Duffull et al., 2015), and all six anticholinergic burden scales have also been used for investigating associations with acute and chronic healthcare use (Campbell, Perkins, & Bradt, 2016; Salahudeen, Hilmer et al., 2015).

Five of the scales include a high proportion of medications available in the US, ranging from 83% (ALS) to 100% (ARS). The ABC scale only includes 67% of medications available in the US. A similar trend was observed among scales with a high proportion of medications observed in the dataset, with the ARS including the highest (100%) and the ABC including the lowest proportion (70%). There is wide variation in the number of medications considered by each scale (n = 27–520) and therefore the distribution of score categories within scales (see Fig. 1 and next section describing scale agreement). For example, although the ADS captures the greatest number of medications (n = 520), 78% of them are low potency anticholinergics, with a score of 0. The percentage of high potency medications captured across the scales also varied from 26% to 81%. The ALS includes the highest proportion of prescription medication (90%), followed by the ABC (85%) and the ADS (83%). The AAS includes the lowest proportion of prescription medications (76%).

3.1.1. Scale agreement

The six scales of interest (AAS, ABC scale, ACB scale, ADS, ALS and ARS) captured different sets of medications, with variations in assigned scores (Supplementary Fig. S1). For example, among common medications with anticholinergic activity, paroxetine is listed on five of the six scales, but with assigned scores of either 1, 2 or 3, while tramadol is listed on two scales with a score of 1 or 2, and levomepromazine is listed on just one scale, but with a score of 3. Similarly, there is wide variability among high-potency medications; e.g., clomipramine has a consistent score of 3 but is listed on only three of the six scales, while ipratropium is assigned a score in two scales of either 0 or 4.

Fig. 2 shows the degree to which scales assign the same anticholinergic score. Overall, the greatest similarity occurred between the ACB scale and ADS; 81 of the 104 medications considered in the ACB scale are also considered in the ADS, and at 0.82, the correlation coefficient between scores derived with these scales was the highest of all the comparisons. While the ADS and ARS exhibited the highest degree of medication overlap (46 of the 49 medications considered in the ARS are also considered in the ADS), the score correlation was 0.68.

3.2. Anticholinergic measures

Two anticholinergic measures, referred to here as “average daily dose” (Campbell et al., 2016) and “cumulative dose” (Gray, Anderson, & Dublin, 2015), were identified in the literature review. The average daily dose measure considers anticholinergic potency of prescribed medications in its estimation but does not consider dose, as it assumes that all patients will receive a daily dose based on label recommendations. It ultimately estimates the average daily anticholinergic exposure over any specified time interval (i.e., exposure period). On the other hand, the cumulative dose measure considers dose in its estimation and it can also be extrapolated over any specified time interval; it does not, however, consider anticholinergic potency. An overview of the features of these measures is provided in Table 1, with more detailed description in the Supplement Text S1.

3.2.1. Average daily dose measure

The average daily dose measure (Campbell et al., 2016) was developed using the ACB scale; however, it can be applied to any of the available scales. It considers duration of and cumulative exposure to anticholinergic agents but has not yet included prescribed dose in its calculation. Score boundaries range from 0 to an upper boundary that depends on the highest score and number of medications included in the employed scale. No suggested categorization of values is provided. The score is independent of follow-up time.

Average daily dose may be calculated by summing the total anticholinergic potency (according to the ACB scale) of all anticholinergics prescribed over the period considered by the ACB scales and dividing the resulting value by the number of days in the period, as follows:

$$\text{Mean total ACB score} = \frac{\sum (\text{Drug A \# days supplied x ACB score}) + (\text{Drug B \# days supplied x ACB score}) + (\text{Drug X...})}{\text{\# days in } \textit{the exposure period}}$$

3.2.2. Cumulative dose measure

The cumulative dose measure (Gray et al., 2015) is not dependent on scale scores; any of the scales may be employed only for determining the medications included in the estimation of the score. This measure was originally used to assess effects of high potency anticholinergics only, but not in any specific disease context (Gray et al., 2015). It considers duration of and cumulative exposure to anticholinergic agents and dose (but not potency). Score boundaries range from 0 to infinity and suggested score categories are based on clinical interpretation and observed score distribution within the study sample. The score is dependent on follow-up time.

To calculate scores based on this measure, medication doses are first standardized and then summed to derive an estimate of cumulative exposure, described as cumulative total standardized daily dose (TSDD) (Gray, LaCroix, & Blough, 2002; Hanlon, Boudreau, & Roumani, 2009). Steps to calculate TSDD are: 1) calculate total medication dose for each prescription dispensation of a medication considered by an anticholinergic scale like the ACB scale, by multiplying the tablet strength by the number of tablets dispensed; 2) for each prescription dispensation, calculate the standardized daily dose (SDD) by dividing the estimated total medication dose by the minimum-effective dose per day (MED) recommended for use in older adults as per Semla et al (Semla, Beizer, & Higbee, 2010); and 3) for each participant, sum the SDD for all

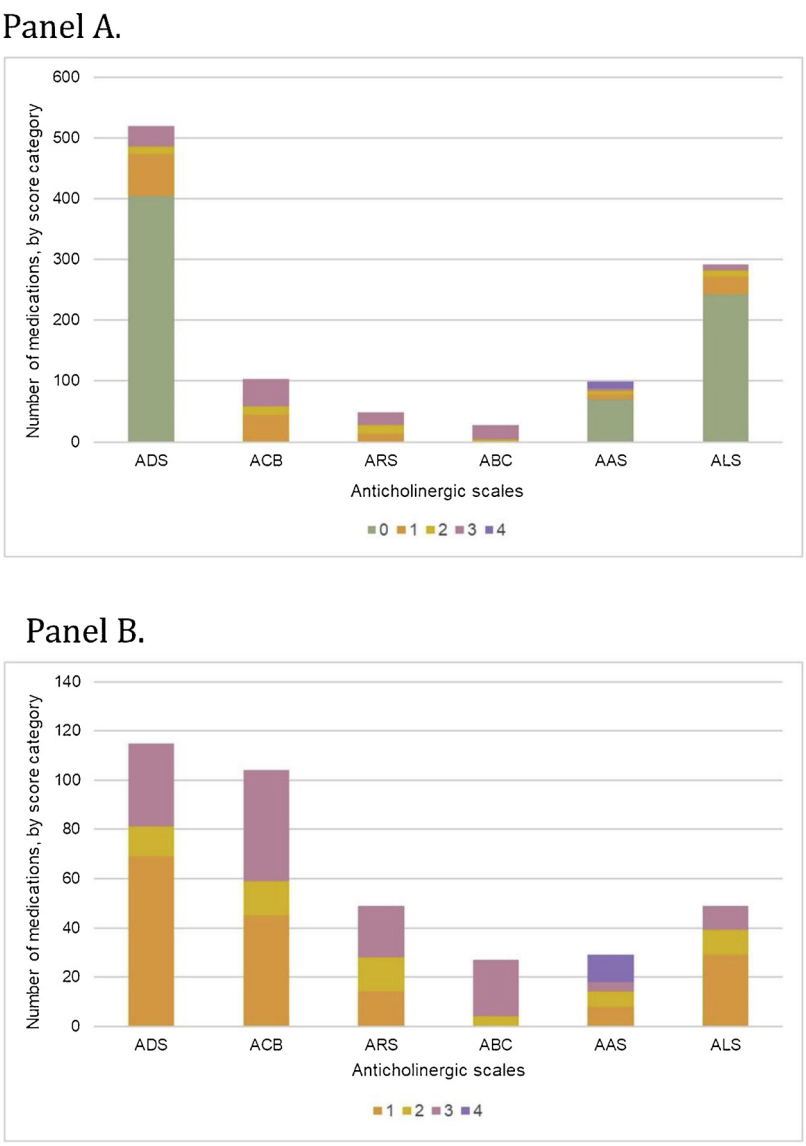

Fig. 1. Number of medications in each score category.
Key: Anticholinergic Activity Scale (AAS); Anticholinergic Burden Classification (ABC); Anticholinergic Cognitive Burden (ACB); Anticholinergic Drug Scale (ADS); Anticholinergic Loading Scale (ALS); Anticholinergic Risk Scale (ARS).
Legend: Distribution of medication scores in each scale, including scores of 0 (Panel A); excluding 0 (Panel B).

anticholinergic pharmacy dispensations during the exposure period to generate a TSDD. The authors of this measure then categorized the resulting TSDD into "no use" (score of 0); 1–90; 91–365; 366–1095; or greater than 1095, with cut points based on clinical interpretability and the observed exposure distribution.

4. Discussion

A number of cross-sectional studies have evaluated the association between anticholinergic burden and poor health outcomes, and a few, including Hsu, Wen, and Chen (2017), and Lu, Wen, and Chen (2015), have used modified approaches to estimating longitudinal exposure, but few have examined the cumulative or prolonged exposure to anticholinergics. The available evidence indicates that cumulative exposure may result in an increased risk of cognitive impairments, incident dementia and falls (Campbell et al., 2016; Gray et al., 2015; Han, Agostini, & Allore, 2008; Richardson, Fox, & Maidment, 2018; Szabo, Gooch, & Schermer, 2019). Given the widespread use of anticholinergics, understanding the burden associated with increased exposure is paramount to avoiding potential medication-related risk, thereby optimizing safety. While administrative databases are readily accessible for research, they still represent an underutilized resource for research into the effects of cumulative anticholinergic exposure. In this study, we comprehensively reviewed six anticholinergic scales and two measures to determine their suitability for assessing anticholinergic burden in observational studies, particularly those relying on administrative data. The scales and measures were found to have distinct characteristics that may influence anticholinergic burden estimates. The performance of a selected scale or measure depends upon both the outcome of interest and the underlying disease profile of the population for which assessment is sought.

Several studies have reviewed and appraised anticholinergic scales currently available. Kersten, Molden, and Tolo (2013), Welsh et al. (2018), Villalba-Moreno et al. (2016), Ruxton et al. (2015), and Salahudeen, Duffull et al. (2015) (2015b) have all conducted systematic reviews in this area, summarizing the characteristics of the different scales that have been used and/or their utility in evaluating adverse outcomes. Other studies have looked at concordance between scales

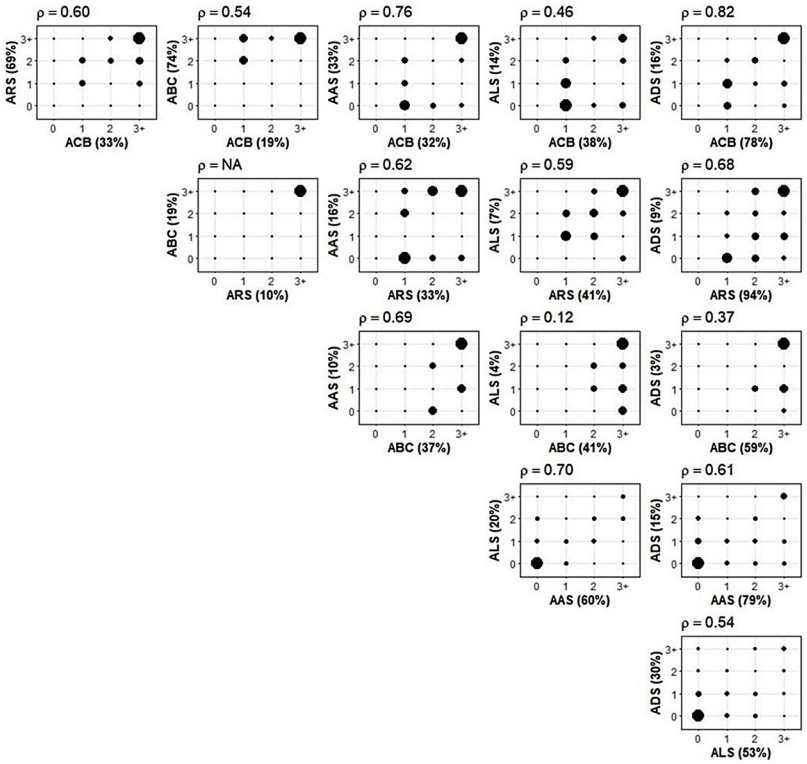

Fig. 2. Score agreement between selected scales.
Key: Anticholinergic Activity Scale (AAS); Anticholinergic Burden Classification (ABC); Anticholinergic Cognitive Burden (ACB); Anticholinergic Drug Scale (ADS); Anticholinergic Loading Scale (ALS); Anticholinergic Risk Scale (ARS)
Legend: Spearman's correlation coefficient between scores for medications common to the two scales are reported above each matrix. The percent of medications given a score by a scale also given a score by the other scale is reported in axes labels.

Table 1
Features of anticholinergic burden measures.

Feature	Average daily score (Campbell et al., 2016)	Cumulative dose (Gray et al., 2015)
Data requirements for implementation in studies informed by administrative datasets		
Medication name	Yes	Yes
Medication dose	No	Yes
Days supplied	No	Yes
Minimum-effective dose	No	Yes (Semla et al., 2010)
Daily dose of dispensed medications	No	No
Developed within the context of a specific disease / condition?	No	No
Built from a specific anticholinergic burden scale?	Yes, ACB scale but can accommodate any scale	No
Can any scale be considered for this measure?	Yes	Not dependent on scale scores, but different scales can be considered for determining the medications that will be included in the estimation of the score. Authors focused on high potency anticholinergics only.
Does it consider duration of exposure?	Yes	Yes, indirectly, by considering total number of tablets dispensed
Does it consider cumulative exposure?	Yes	Yes
Does the calculation consider dose?	No	Yes
Does it consider residual anticholinergic effect?	No	No
What does the measure estimate	Average daily anticholinergic exposure	Cumulative total standardized daily dose
Score boundaries	lower bound: 0 upper bound: depends on the highest score of the scale considered, and the total number of medications in the scale (theoretical upper bound)	lower bound: 0 upper bound: infinity (theoretical upper bound)
Suggested score categories	0: 0 – 0.49; 1: 0.50 to 1.49; 2: 1.50 to 2.49; etc.	no use; 1 to 90; 91 to 365; 366 to 1095; greater than 1095
Method for determining score categories	Arbitrary	Based on clinical interpretability and the observed exposure distribution within the study sample
Score depends on length of study period?	No	Yes

Key: Anticholinergic Cognitive Burden scale (ACB).

when applied to claims data (Mayer et al., 2017; Salahudeen, Hilmer et al., 2015) and community-dwelling populations (Naples et al., 2015), but none assessed the suitability of the scale in regard to the population under review prior to its application. As scales are developed under different circumstances in order to best meet the needs of the developers and the populations to which they are applied, there is no scale that is best suited across all circumstances. To that end, our review provides future researchers recommendations on which scales to use when evaluating anticholinergic burden in observational studies relying on administrative data. Here we identified six anticholinergic scales as suitable for determining individual cross-sectional estimates of anticholinergic burden. Of these, the ACB scale, ADS and ARS have been widely applied among older adults and are user-friendly in clinical practice. The ADS and ARS both accommodate dose adjustments, and

the ARS has been tested with a wide range of clinical parameters. The range of medications covered varies across scales, with the ADS considering the greatest number of medications. As the ACB scale and the ADS considered the greatest number of medications, have been validated and demonstrated the greatest inter-scale agreement (0.82), both were considered suitable for implementation in observational studies where anticholinergic exposure needs to be quantified.

The primary limitations of these scales are that they do not consider systemic drug exposure, distribution in the brain or drug interactions. The ABC scale, AAS and ALS are based on serum anticholinergic activity, giving them biological precision. However, although an association between high serum anticholinergic activity levels and both cognitive and functional impairments have been demonstrated in observational studies (Tollefson, Montague-Clouse, & Lancaster, 1991), there is poor correlation between this measure and central adverse effects. Additionally, prospective studies have observed no association between serum anticholinergic activity and cognitive impairment (Tollefson et al., 1991). Notably, the ABC scale, AAS, and ALS have not been validated and do not take dosing into account. An important factor influencing the choice of scale for estimating anticholinergic burden from retrospective data is the variability in classification of medication score between scales that may translate to different findings depending on the population or disease investigated. For example, quetiapine, an antipsychotic medication, is listed in one scale as having no anticholinergic properties, whereas others list it with a score of 1, 2 or 3. If the prevalence of quetiapine prescription among the population of interest is high, varying estimates of anticholinergic exposure will be produced due to the variation in score for this medication. Similarly, study selection criteria that allow higher or lower representation of medications with anticholinergic activity may also influence results, as could over-the-counter product use among the population of interest, as this is not necessarily captured in an administrative database. Selection criteria could also affect results in cases where pre-existing cognitive dysfunction is present, as results may be exacerbated by relatively small levels of anticholinergic exposure. Finally, availability of medications varies by country. For studies relying on data from a different country than that in which the scale was developed, attention should be paid to the medication coverage of the selected scale in the jurisdiction of interest as well as medication coverage within the patient population under study. For this last reason, it was important for the present evaluation to be limited to a single jurisdiction (i.e. US) in order to provide researchers recommendations that could be generalized to observational studies focusing on patient populations within the US.

With respect to identified measures, key differences between the average daily dose and cumulative dose measures are that the average daily dose does not consider prescribed dose in its calculation. Conversely, although the cumulative dose measure does include prescribed dose, it does not account for the anticholinergic potency of the medications. We considered this important, as we hypothesize that by only considering these properties individually in the measure calculations, the potential impact of the interaction between patient-specific dosing and anticholinergic activity may be missed. Despite these limitations, we considered both measures appropriate for implementation in observational studies where anticholinergic exposure is measured over time. It should be noted that relevant categorical or binary cut-point thresholds for each measure may vary depending upon the clinical outcome of interest. Currently, intended study outcomes have been used to define thresholds for burden scores; however, these may need to be adjusted to reflect clinical significance of anticholinergic burden on different outcomes. A major limitation in estimating anticholinergic burden from administrative data is the inability to measure medication adherence; although lack of adherence may be partially accounted for by observation of a reduction in frequency of prescription refill, specific timing of medication ingestion cannot be confirmed.

5. Conclusions

In a comparison of the properties of six anticholinergic scales we determined that the ACB scale and ADS were well suited for implementation in observational studies where anticholinergic exposure needs to be quantified, as they consider the largest number of medications and were validated with adverse clinical outcomes. The relevance of the ACB scale and ADS is demonstrated by their development within a general population, and previous application in administrative data. Average daily dose and cumulative dose measures were both considered appropriate measures for quantifying cumulative anticholinergic exposure; however, both are limited in scope due to their lack of consideration of dose or potency, respectively. Development and validation of methodology that longitudinally captures both aspects of anticholinergic treatment are needed.

Conflict of interest

Daniel Ng = Employee of Astellas Pharma Global Development, Inc.

Greta Lozano-Ortega, Antoinette Cheung, Karissa Johnston = Employees of Broadstreet Health Economics & Outcomes Research, which received payment from Astellas to conduct the study.

Roger Dmochowski, Noll Campbell and Adrian Wagg = Received payment from Astellas for consultation services in the conduct of this study.

Author contributions

All authors contributed to the drafting or revisions of the manuscript and have read and approved the final version of this submitted manuscript. All authors fulfill the ICMJE guidelines for authorship.

Sponsor's role

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.archger.2019.05.010.

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