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Assessment and comparison of anticholinergic exposure in older adults at a Basic Health Unit in Porto Alegre

Avaliação e comparação da exposição anticolinérgica em idosos de uma Unidade Básica de Saúde de Porto Alegre

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Abstract

Objectives: To estimate the anticholinergic burden in geriatric patients using two scales and to assess the degree of agreement between them.

Methods: Data from an observational study conducted in a primary health care service were used. Anticholinergic burden was assessed using the Belgian Scale Muscarinic Acetylcholinergic Receptor Antagonist Exposure Scale and the Brazilian Scale of Medicines with Anticholinergic Activity. The cumulative anticholinergic burden score was classified using a categorical approach: Brazilian scale (0: none; 1–2: low; ≥ 3 : high) and Belgian scale (0: none; 0.5–1.5: low; ≥ 2 : high). The degree of agreement between the two instruments was obtained through Cohen's kappa coefficient.

Results: A total of 374 older people were included, most of them female and aged between 60 and 69 years. At least one potentially inappropriate drug with anticholinergic activity was used by 60.70% of patients according to the Brazilian scale and 32.89% by the Belgian scale. On average, 20.85% were under high anticholinergic exposure. Overall, on both scales, the most commonly recurrent medications were those indicated for the treatment of psychiatric disorders. Agreement between the scales was moderate (Kappa = 0.43).

Conclusions: A high percentage of older adults was exposed to drugs with an anticholinergic burden, posing risks to health and quality of life. Consensus is needed on how anticholinergic burden is calculated by these scores, as well as standardization of the list of included drugs.

Keywords: potentially inappropriate medication list; cholinergic antagonists; aging; primary health care.

Resumo

Objetivos: Estimar a carga anticolinérgica em idosos com base em duas escalas e avaliar o grau de concordância entre estas.

Metodologia: Foram utilizados dados de um estudo observacional realizado em um serviço de atenção primária. A carga anticolinérgica foi avaliada pela escala belga *Muscarinic Acetylcholinergic Receptor Antagonist Exposure Scale* e da Escala Brasileira de Medicamentos com Atividade Anticolinérgica. A pontuação da carga anticolinérgica cumulativa foi classificada utilizando uma abordagem categórica: escala brasileira (0: nenhuma, 1–2: baixa, ≥ 3 : alta) e escala belga (0: nenhuma, 0,5–1,5: baixa, ≥ 2 : alta). O grau de concordância entre as duas ferramentas foi obtido por meio do coeficiente Kappa de Cohen.

Resultados: Foram incluídos 374 idosos, a maioria do sexo feminino e com idade entre 60 a 69 anos. O uso de pelo menos um medicamento potencialmente inadequado com atividade anticolinérgica foi verificado em 60,70% dos idosos com a aplicação da escala brasileira e em 32,89% com a escala belga. Em média, 20,85% estavam sob alta exposição anticolinérgica. De modo geral, os medicamentos mais recorrentes, para ambas as escalas, foram os indicados para o tratamento de transtornos psiquiátricos. A concordância entre as escalas foi moderada (Kappa = 0,43).

Conclusão: Um percentual elevado de idosos estava exposto a medicamentos com carga anticolinérgica, representando riscos para a saúde e a qualidade de vida. É necessário um consenso sobre como calcular a carga anticolinérgica nos diferentes escores, bem como a padronização da lista de medicamentos incluídos.

Palavras-chave: lista de medicamentos potencialmente inadequados; antagonistas colinérgicos; idoso; atenção primária à saúde.

INTRODUCTION

According to the World Health Organization (WHO), older persons already account for a significant proportion of the world population and, by 2030, one in every six people will be 60 years old or older as population aging tends to continue growing over time.¹ These data highlight the need for greater attention to healthy aging.

The aging process causes major physiological changes in the human body, making older adults more susceptible to multimorbidity (also known as polypathology), adverse drug reactions (ADRs), and toxicity. Consequently, polypharmacy, often defined as the simultaneous use of four or more drugs, becomes the main strategy for treatment of this multiple burden of diseases. In this scenario, it is important that health care providers, particularly pharmacists, monitor the safety of prescribed drugs, adopt pharmacotherapy review strategies, work alongside other health care professionals and elder care providers, and use evidence-based clinical decision-making. In addition, it is expected that they devote attention to the practice of self-medication, especially when dealing with potentially inappropriate medications (PIMs) for older adults.²⁻⁴

Prescription of PIMs, such as drugs with anticholinergic activity, may contribute to the onset of adverse events and offer health risks. These drugs are often associated with higher rates of hospitalization, comorbidities, and deaths among older persons, resulting in expenses for the health system and reduced quality of life. This is particularly relevant considering that these individuals are already facing a loss of functional capacity, which may hinder performance of the activities of daily living.⁵⁻⁷

The mechanism of action of anticholinergic drugs, also known as parasympatholytics, is mediated by acetylcholine, a neurotransmitter that plays key roles in cognition, learning, and memory. Inhibition of acetylcholine activity produces adverse effects on both the central nervous system, including confusion, delirium, and hallucinations, and in the peripheral nervous system, such as constipation, urinary retention, blurred vision, gastric disorders, and xerostomia.^{3,8} In older adults, anticholinergics may also be associated with serious clinical outcomes such as agitation and cognitive impairment, in addition to an increased risk for the development of neurodegenerative diseases, including Alzheimer's disease.^{9,10}

Drugs with anticholinergic action should preferably be avoided in older adults or have their dose reduced, due to cumulative effects.¹¹ Cumulative exposure due to concomitant use of more than one drug with anticholinergic properties is referred to as anticholinergic burden, which can be assessed using scales that measure the risk and severity of ADRs.^{4,10}

Estimated anticholinergic burden may vary according to the instrument used for calculation. The Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale,¹² developed in Belgium, considers not only the potency of anticholinergic drugs but also the daily dosage used by the patient. On the other hand, the Brazilian Scale of Medications with Anticholinergic Activity¹³ considers only anticholinergic potency for the calculation. This difference may result in a higher accuracy of the Belgian scale in defining the anticholinergic burden of older adults. However, there are no data in the literature comparing these two scales in a primary-care setting, nor assessing the differences in the calculated anticholinergic burden. Studies with this purpose might help providers choose the ideal scale for calculating anticholinergic load when evaluating prescriptions.

Within this context, the present study was designed to estimate and compare the anticholinergic burden among geriatric patients at a Basic Health Unit in the city of Porto Alegre, Brazil, using two different scales, and to assess the degree of agreement between these instruments.

METHODS

Data were obtained from a previous cross-sectional study with retrospective data collection, conducted with a similar objective.¹⁴ This study reviewed the electronic medical records of 390 older adults chosen by simple random sampling who had been treated between March and May 2018 at a Basic Health Unit affiliated with a university hospital in the city of Porto Alegre, Brazil.

The inclusion criteria were older adults (aged ≥ 60 years as per the Brazilian legal definition)^{15,16} attending the Basic Health Unit who were on at least one medication. Patients with medical records that did not contain information on sex, age, diagnosed diseases, current medications, and daily dosage of medications were excluded from the sample.

The study was approved by the Ethics Committee of *Hospital das Clínicas de Porto Alegre* (opinion no. 2,466,939). The EQUATOR Network guideline for reporting observational studies was followed.

The anticholinergic burden of each patient was assessed using two scales: the Belgian Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale (MARANTE)¹² and the Brazilian Scale of Drugs with Anticholinergic Activity (*Escala Brasileira de Medicamentos com Atividade Anticolinérgica* – EBMA).¹³ The main difference between the scales is the constitution of the calculated anticholinergic burden: while the MARANTE considers both dosage and anticholinergic potency, the EBMA takes only potency into account. However,

the Belgian scale is limited to only 41 active substances out of 100 anticholinergics available internationally, while the Brazilian scale covers a greater number of drugs ($n = 125$). Lastly, the classification of anticholinergic exposure also differs between the two scales because the choice of method for attributing the anticholinergic potency of each drug was based on expert consensus, which may vary depending on the judgment of professionals in the field.

Despite the scales including different medications, we decided to carry out an analysis of agreement based on the hypothesis that the assessment of anticholinergic exposure by the two scales would be compensatory: if, on the one hand, the Brazilian scale includes a greater number of drugs, the Belgian scale considers daily dosage in its assessment.

The anticholinergic burden variables for dosage and potency were assessed only for the MARANTE scale, with dosage divided into four ranges: very low (Below GminEV – minimal geriatric effective value), low (above GminEV), high (above GMainD – geriatric maintenance dosage), and very high (above GMaxEV – maximum geriatric effective value); and potency dichotomized as low, when equal to 1, or high, when equal to 2.

Due to the peculiarity of the Belgian scale considering the dosage of prescribed drugs, 16 medical records that did not contain this information were not analyzed, and 46 drugs that contained only dosage information were considered as QD use (once daily). Thus, the total sample analyzed was 374 patients. Additionally, medications used irregularly or sporadically were considered in the analysis, so that the entire prescription was assessed.

The anticholinergic burden was calculated as follows: for the MARANTE scale, by multiplying the tabulated value of each drug's anticholinergic potency (either 1 or 2) by the value attributed to each dosage range (0.5, 1, 1.5, or 2). The dosage range value depends on the daily dosage consumed and is classified as low, moderate, high, or very high depending on the drug. Finally, the overall anticholinergic load is obtained as the sum of the individual values of the anticholinergic burden of each drug present in the prescription. As for the Brazilian scale, one need only add the tabulated anticholinergic potency scores (1, 2, or 3) of each drug present in the prescription to obtain the overall anticholinergic load.

The cumulative anticholinergic burden score was classified using a categorical approach for both scales: for the Brazilian Scale, 0: none, 1 – 2: low, ≥ 3 : high; for the Belgian scale, 0: none; 0.5 – 1.5: low; ≥ 2 : high.

It bears stressing that the classification of anticholinergic exposure is different between the scales due to the

choice of expert consensus method used by the authors of the scales^{12,13} to obtain classification of anticholinergic potencies and, in the case of the Belgian scale, dosage ranges of each drug. On the Brazilian scale, for example, the drug tolterodine has an anticholinergic potency equal to 3, whereas on the Belgian scale, the same drug has a potency equal to 2. Therefore, the estimated degree of anticholinergic exposure differs between the tools.

The degree of agreement between the two anticholinergic burden scales was obtained using Cohen's kappa coefficient (> 0.75 , high agreement; $0.40 - 0.75$, moderate agreement; < 0.40 , low agreement),¹⁷ including drugs that did not appear on both scales and those that did not show anticholinergic activity. Data were analyzed in PASW Statistics version 18.00 software.

RESULTS

The sample population consisted of 374 older people, most of whom were female (63%) and aged between 60 and 69 years (43%). According to a previous publication by our research group, age 60 to 80 years (representing the younger older adult population) and female sex were associated with high anticholinergic risk.¹⁴

As shown in Table 1, according to the Brazilian scale, 60.70% of the patients used at least one PIM with anticholinergic activity, compared to 32.89% on the Belgian scale. According to both tools, on average, 20.85% of the sample

TABLE 1. Anticholinergic load profile and use of potentially inappropriate medications in the older population treated at a Basic Health Unit, Porto Alegre, Brazil, 2018 ($n = 374$).

Rating	MARANTE scale	Brazilian scale
	n (%)	n (%)
Use of at least one PIM	123 (32.89)	227 (60.70)
No anticholinergic activity	251 (67.11)	147 (39.30)
Degree of anticholinergic exposure		
Low	60 (16.04)	134 (35.83)
High	63 (16.84)	93 (24.87)
Anticholinergic potency		
Low	130 (34.76)	
High	58 (15.51)	
Dosage		
Below GminEV (very low)	11 (2.94)	
Above GminEV (low)	54 (14.44)	
Above GMainD (high)	82 (21.93)	
Above GMaxEV (very high)	21 (5.61)	

PIM: Potentially inappropriate medications for older adults.

had a high burden of anticholinergic exposure, and almost twice as many prescriptions in the Brazilian scale had a low degree of exposure compared to the Belgian scale. On the Belgian scale, most drugs showed low anticholinergic potency (34.76%), but there was a higher prevalence of drugs with high dosages (21.93%).

Table 2 presents the five drugs with anticholinergic activity most used by the older population in the study, each one presented a frequency of around 40 times. According to the Brazilian scale, the most widely used medications with anticholinergic effect belonged to the classes of beta-blockers,

diuretics, and antidepressants; for the Belgian scale, drugs indicated for the treatment of psychiatric disorders were the most recurrent. The drugs were classified according to the Anatomical Therapeutic Classification (ATC) system developed by WHO.¹⁸

The variation in the total score of prescriptions ranged from 0 to 8 on the Brazilian scale (Figure 1) and 0 to 7.5 on the Belgian scale (Figure 2).

The level of agreement between the tools, considering the use of at least one PIM, was classified as moderate (Kappa = 0.43).

TABLE 2. The five drugs with anticholinergic activity most often used by the older population treated at a Basic Health Unit, Porto Alegre, Brazil, 2018 (n = 374).

Brazilian scale			
ATC/DDD	Drug	Anticholinergic potency	n (%)
C07AB03	Atenolol	1	47 (12.57)
N06AB03	Fluoxetine	1	43 (11.50)
C07AB02	Metoprolol	1	39 (10.43)
N06AA09	Amitriptyline	3	39 (10.43)
C03CA01	Furosemide	1	26 (6.95)
MARANTE scale			
ATC/DDD	Drug	Anticholinergic potency	n (%)
N06AB03	Fluoxetine	1	43 (11.50)
N06AA09	Amitriptyline	2	39 (10.43)
N06AB04	Citalopram	1	20 (5.35)
N03AE01	Clonazepam	1	18 (4.81)
N06AB10	Escitalopram	1	9 (2.41)

ATC: anatomical therapeutic classification; DDD: defined daily dose.

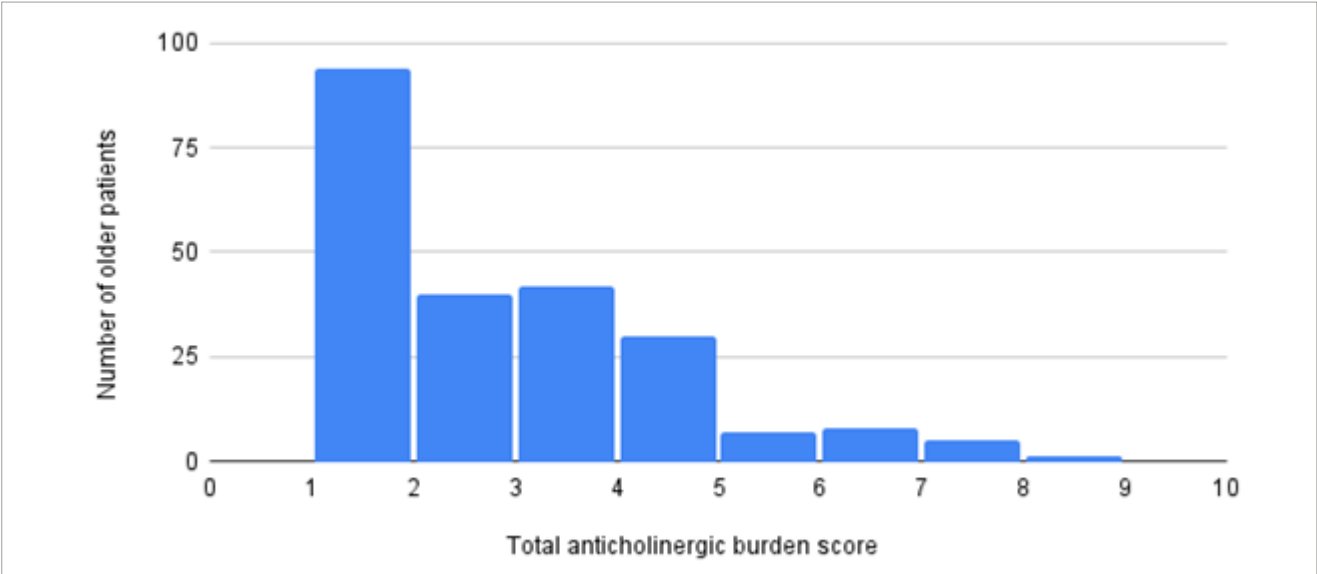


FIGURE 1. Distribution of anticholinergic burden scores on the Brazilian scale in the older population studied.

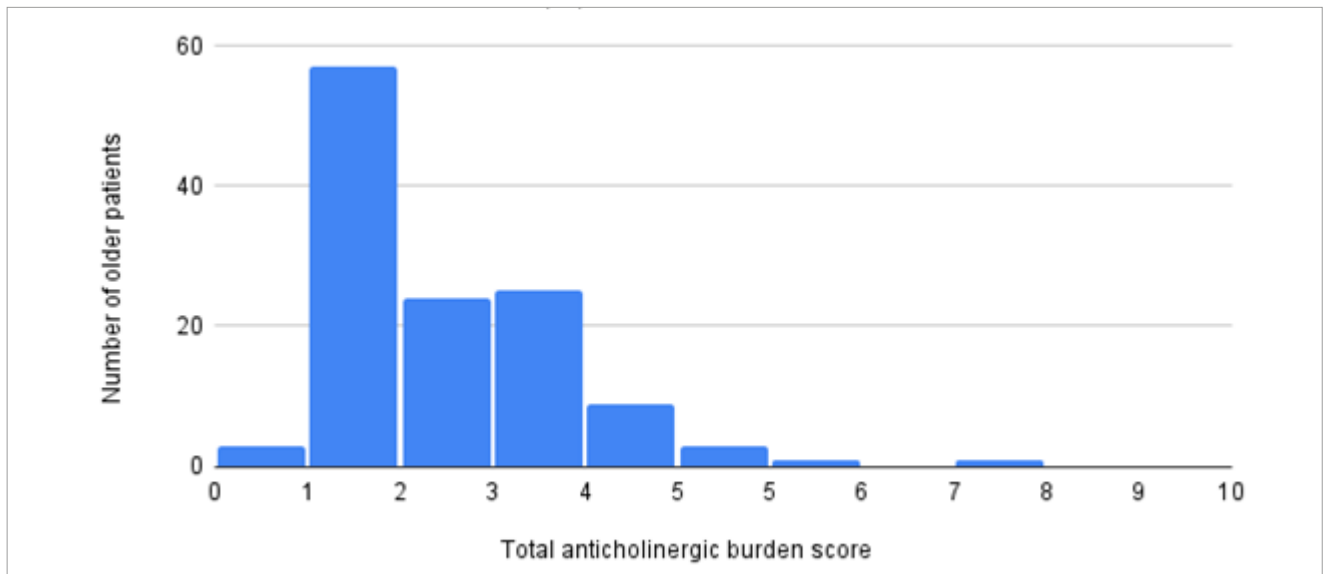


FIGURE 2. Distribution of anticholinergic burden scores on the MARANTE scale in the older population studied.

DISCUSSION

Application of the two scales disclosed that a high percentage of older adults (32.89% according to the Belgian scale and 60.70% according to the Brazilian Scale) were exposed to drugs with anticholinergic activity, posing risks to the health and quality of life of these individuals. Other studies have shown similar results. Using the Belgian scale, studies carried out in Belgium revealed that 31.80 to 45.00% of the studied populations were exposed to drugs with anticholinergic activity,^{12,19,20} compared to 58.45% according to the Brazilian scale in a study with patients from an inpatient unit carried out in Switzerland.²¹

Although the Belgian scale may provide more accurate anticholinergic burden estimation by combining anticholinergic dosage and potency, the analysis is limited to only 41 active substances out of the 100 anticholinergics available internationally. On the other hand, the Brazilian scale has a greater number of drugs available for analysis ($n = 125$). In addition, the fact that it was developed from a cohort of older people in Belgium makes it difficult to generalize to the Brazilian population.

Furthermore, the cutoff points assigned to classify anticholinergic exposure were different for the analyzed scales, which may be attributed to differences in judgment of the magnitude of anticholinergic effect by the expert consensus. In the population studied, according to the criteria of Nery and Reis, approximately twice as many patients (60.70%) were using at least one PIM with anticholinergic activity as when using the MARANTE scale (32.89%). Such differences were also found in other studies.²²⁻²⁴ Trisancho-Pérez et al.²⁴ observed variations ranging from 13.80 to 57.50%

in the percentage of drugs considered to have anticholinergic activity among 10 analyzed scales, as well as for the proportion of patients at risk of developing major adverse effects, which ranged from 71.10 to 9.70%, demonstrating the extensive variability between these scales. It should be noted that this lack of uniformity in cutoff points may omit or overestimate patients at risk of developing adverse effects, subsequently causing variation in clinical outcomes such as mortality and hospitalization.

Although we observed differences between the two scales, the kappa coefficient showed moderate agreement, which suggests greater applicability of the Brazilian Scale due to its practical nature, especially in clinical practice, as it is not necessary to assign values for each dose range.

In comparison with other studies, the results obtained for the Belgian Scale were similar: In a study conducted in primary care,¹⁹ but with people over 80 years of age and analyzing only chronic prescription medications, the authors noted that 16.10% of the sample had a low anticholinergic exposure and, similarly, 15.70% a high exposure. As was the case in this study, drugs with low anticholinergic potency and a dose considered high were the most widely consumed, accounting for 80.00 and 51.50%, respectively. Moreover, the frequency of medications with a score of at least 0.5 on the scale was 31.80%, with scores ranging from 0 to 7.

In a pilot study conducted in Belgium, 33.10% of 148 patients over 65 years of age were found to have a high anticholinergic burden²⁵ — almost twice as much as in our sample (16.84%). This discrepancy may be associated with the inclusion of patients residing in long-term care institutions, as well as the selection

of older people with at least 3 months of life expectancy. These factors may have been associated with a greater need for medication prescription, particularly of anticholinergics.

Using the Brazilian scale as a measure to assess anticholinergic exposure, a Swiss study found that 30.06, 28.39, and 41.55% of older patients had high, low, and no anticholinergic exposure, respectively,²¹ results similar to those found for our population (24.87, 35.83, and 39.30% for high, low, and no exposure, in that order).

According to the histograms of the Brazilian and Belgian scales (Figures 1 and 2, respectively), a considerable proportion of the older adults in the sample had an anticholinergic burden equal to one, classified as low. Nevertheless, it is crucial to consider the cumulative effect of these drugs, as even low anticholinergic exposure can be associated with substantial risk of adverse events.²⁶ Prescription interventions by health care providers are crucial in this respect and may contribute to reducing the number of PIMs taken.¹⁹

To the best of the authors' knowledge, this is the first study to compare the Belgian and Brazilian scales, considering the recent development of these instruments. Strengths of our study included a broad assessment of anticholinergic exposure, which included chronic, occasional, and sporadic use. The sample size is also consistent with other data in the literature on this topic.

Limitations included omission of intervals between doses for several drugs because the data collected from the original study was retrospective. Thus, these prescriptions were accounted as once-daily (QD) doses. Furthermore, there was no standardization of the classes of drugs present in the two scales. Recalculation of the agreement test covering only those drugs included in the two lists would be an alternative to assess the agreement between the lists more accurately. Finally, the data used herein were obtained from a previous

study carried out in a Basic Health Unit connected to a university hospital, which may have restricted the medications to those covered by the municipal medication list.

CONCLUSION

Further studies assessing the agreement between anticholinergic risk scales and the prevalence of use of drugs with anticholinergic activity older adults are needed, especially to ascertain whether including doses in these scales provides greater precision when estimating anticholinergic burden.

A high percentage of the older patients were exposed to drugs with anticholinergic activity, and, on average, 20% were exposed to a high anticholinergic burden, posing risks to these individuals' health and quality of life. Additionally, consensus is needed on anticholinergic burden scores and standardization of the list of included drugs.

DECLARATIONS

Conflict of interest

The authors declare no conflict of interests.

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Author's contribution

TSS: conceptualization, data curation, formal analysis, methodology, software, writing – original draft. TSG: project administration, supervision, visualization, writing – review & editing. IH: methodology, project administration, software, supervision, visualization, writing – review & editing.

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