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Analysis of drug scale with anticholinergic activity

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Abstract

Objective: To identify the anticholinergic drug scales and analyze agreement regarding the drugs included. **Methods:** This is a descriptive study on scales for of drugs with anticholinergic activity. The scales were identified through bibliographical research. The drugs presented in the scales and the systematic classification of the anticholinergic activity scores were identified. The drugs included in the scales that were registered with the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária*, ANVISA) were verified. The drugs included were recorded in an Excel spreadsheet and were classified according to Level 3 of the systematic Anatomical Therapeutic Chemical (ATC) classification proposed by the World Health Organization (WHO). A *Kappa Fleiss* analysis was performed to assess agreement between the scales in relation to the drugs present in them. The scales were compared according to the *Kappa Cohen* statistics. **Results:** A total of 25 anticholinergic activity measuring scales were identified. The most recent scale with the largest number of drugs is the *Crideco Anticholinergic Activity Scale* (CALS). The *Anticholinergic Burden Classification* (ABC) has a smaller number of drugs. Regarding the scoring system, most scales use scores from 0 to 3. 347 synthetic drugs and two plant extracts (belladonna and *scopolia*) were identified in the scales. The extracts were considered in this study to be natural products, considering the plant type present in the extract. To calculate the total number of drugs present in the scales, a total of 349 was taken into account. The most frequent drugs were from subgroups N06A- antidepressants, N05B- anxiolytics and A02B- drugs for peptic ulcer and gastroesophageal reflux disease. The most prevalent pharmacological subgroups were as follows: N06A- antidepressants, N05A - antipsychotics and R06A - antihistamines. Most of the drugs present in the scales had indirect anticholinergic activity. According to the *Kappa Cohen* statistics, only 10 pairs of scales showed moderate agreement. **Conclusion:** There are 25 scales available for measuring anticholinergic activity. There is consistent agreement between the identified scales regarding the drugs included. Considering the drugs included and the pairs of scales, weak and fair agreement prevailed.

Keywords: scales, cholinergic antagonists, muscarinic antagonists, anticholinergic burden

Análise das escalas de fármacos com atividade anticolinérgica

Resumo

Objetivo: Identificar as escalas anticolinérgicas e analisar a concordância em relação aos fármacos incluídos. **Métodos:** Trata-se de um estudo descritivo relativo às escalas de fármacos com atividade anticolinérgica. As escalas foram identificadas através de uma pesquisa bibliográfica. Identificou-se as escalas de mensuração da atividade anticolinérgica, coletou-se os fármacos presentes e a sistemática de classificação do escore da atividade anticolinérgica. Verificou-se os fármacos incluídos nas escalas que apresentavam registro na Agência Nacional de Vigilância Sanitária (ANVISA). Os fármacos incluídos foram registrados em uma planilha Excel e classificados segundo o nível 3 da sistemática da *Anatomical Therapeutic Chemistry* (ATC) da Organização Mundial da Saúde (OMS). Realizou-se análise de *Kappa Fleiss* para avaliar a concordância entre as escalas em relação aos fármacos presentes. As escalas foram comparadas segundo a estatística *Kappa Cohen.* **Resultados:** Foram identificadas 25 escalas de mensuração da atividade anticolinérgica. A escala com maior número de fármacos e mais recente é a *Crideco Anticholinergic Activity Scale* (CALS). A *Anticholinergic Burden Classification* (ABC) possui menor número de fármacos. Em relação à sistemática de pontuação a maioria das escalas usa um escore de 0 a 3. Nas escalas foram identificados 347 fármacos sintéticos e dois extratos vegetais (Beladona e *Scopolia*). Os extratos foram considerados nesse estudo como produto natural, considerando o tipo de planta presente no extrato. Para fins de totalização de números de fármacos presentes nas escalas considerou-se 349. Os fármacos mais frequentes eram do subgrupo N06A- antidepressivos, N05B- ansiolíticos e A02B- fármacos para úlcera péptica e doença do refluxo gastresofágico. Os subgrupos farmacológicos mais prevalentes foram: N06A - antidepressivos, N05A- antipsicóticos e R06A- anti-histamínicos. A maioria dos fármacos presentes nas escalas possuíam atividade anticolinérgica indireta. De acordo com a estatística *Kappa Cohen* apenas 10 pares de escalas apresentaram concordância moderada. **Conclusão:** Encontra-se disponível 25 escalas para mensuração da atividade anticolinérgica. A concordância entre as escalas identificadas quanto aos fármacos incluídos é regular. Considerando os fármacos incluídos e os pares de escalas, predominou-se a concordância fraca e regular.

Palavras-chave: escalas, antagonistas colinérgicos, antagonistas muscarínicos, carga anticolinérgica

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Introduction

Drugs with anticholinergic effects block binding of acetylcholine to muscarinic receptors in the central and peripheral nervous system. There are five subtypes of muscarinic receptors, designated as M1, M2, M3, M4 and M5[1]. Most drugs lack selectivity for the different receptor subtypes. Atropine and oxybutynin are examples of drugs that present intrinsic or direct anticholinergic activity; however, there are also others that, in addition to muscarinic receptors, bind to other receptors, exerting agonist or antagonist effects as the main mechanism of action. In the clinical practice, these drugs are prescribed with therapeutic indications unrelated to antimuscarinic activity, but it is important to highlight that they have indirect anticholinergic activity. Drugs with indirect anticholinergic activity include tricyclic antidepressants, antipsychotics and antihistamines[2,3].

Anticholinergic drugs are commonly used for various clinical conditions, especially in older adults. These drugs can induce adverse reaction at the central (memory impairment, drowsiness, dizziness, mental confusion, amnesia, cognitive impairment, inattention, agitation, disorientation, ataxia, hallucinations, delirium, seizures and hyperreflexia) and peripheral (xerostomia, mydriasis, constipation, urinary retention and increased heart rate) levels[2]. There is diverse evidence that the increase in anticholinergic adverse effects among older adults can cause unfavorable clinical outcomes[4,5]. The manifestation and severity of the adverse reactions depend on the anticholinergic pharmacotherapy burden and on each person's sensitivity[6].

The anticholinergic burden is a consequence of the cumulative effect of one or more drugs with direct or indirect anticholinergic activity[7]. The anticholinergic burden calculation is performed with the identification of all drugs prescribed and used by the patient, which have anticholinergic activity. Subsequently, a score is assigned to each drug and these scores are added up[8]. High scores indicate higher risks for adverse events. In older adults, high cumulative anticholinergic burdens are more frequent as a result of using multiple drugs with low anticholinergic activity than using drugs with high activity[9]. It is crucial that health professionals have access to a validated instrument to measure this burden, minimize negative effects and assess risks, considering the wide anticholinergic drug use in the clinical practice[2,5].

There are some measures to quantify anticholinergic activity, such as serum determination (SAA – *Serum Anticholinergic Activity*) and the drug's *in vitro* affinity with the muscarinic receptor. However, the methods used to determine these measures are time-consuming and expensive, thus limiting their use. Alternatively, anticholinergic activity scales through consensus of experts and clinical experience were developed[7,10]. An example is the *Drug Burden Index*, an equation that calculates exposure to anticholinergic drugs and sedatives, based on the dose-response and maximum effect principles[2,3].

Currently, there is diversity of scales for evaluating anticholinergic activity, which are considered reproducible, economical and easy-to-apply instruments. However, the scales vary as to the methods, number of drugs included, each drug anticholinergic activity magnitude, measurement and discrepancies in the validation process[2]. Variability and disagreement between the scales is a limiting factor for their use. A universal method for assessing the anticholinergic burden of drugs has not yet been developed.

Anticholinergic burden is a modifiable risk factor; therefore, it has wide application in the care of older adults. The availability of anticholinergic activity scales contributes to the performance of pharmacists and of the other interdisciplinary team members. It is an important resource for promoting safe drug prescription and for the deprescription process. Integration with pharmacotherapeutic monitoring of older adults provides greater safety in pharmacotherapy.

Considering the above, the objective of the current study was to identify the available anticholinergic scales and to analyze agreement between the scales in relation to the drugs they analyze.

Methods

A descriptive and agreement study was conducted to examine the scales for drugs with anticholinergic activity. The scales were identified through a literature search using the following English terms: "*cholinergic antagonists*", "*anticholinergic*", "*anticholinergic agents*" and these descriptors: "*nicotinic antagonists*", "*muscarinic antagonists*", "*atropinic*", "*scale*", "*load*", "*burden*", "*risk*", "*exposure*" and "*medication*". The search strategy was elaborated using the *AND* and *OR* Boolean operators, and the database searched was *Medline*. The research was limited to articles in English, conducted from January 2020 to April 2022. Scales that did not provide the drug lists and their respective scores, such as *Whalley's Scale*[11] and the *Anticholinergic Burden Score*[12], were excluded from this study.

After identifying the scales, the drugs present in them and the anticholinergic activity score systematic classification were collected. The scale development process and the country were identified. The drugs included in the scales that were registered with the National Health Surveillance Agency (ANVISA) were verified. To elaborate the drug list, presence of synonyms was identified, maintaining the international common name.

An Excel® spreadsheet was prepared to record the drugs and other characteristics included in each scale. The drugs were classified according to Level 3 of the *Anatomical Therapeutic Chemistry* (ATC) system proposed by the World Health Organization (WHO). The spreadsheet was exported to the *Statistical Package for the Social Science* (SPSS) 25.0 software.

A *Kappa Fleiss* analysis was performed to evaluate agreement between the scales in relation to the drugs present in them. The scales were compared in pairs in relation to presence of the drugs, according to the *Kappa Cohen* statistics. The agreement degree will be interpreted according to Landis and Koch (1977): <0.00 - Poor; from 0.00 to 0.20- Weak; from 0.21 to 0.40- Fair; from 0.41 to 0.60- Moderate; from 0.61 to 0.80- High; and from 0.81 to 1.00 - Almost perfect[13].

Results

The database search identified 1,025 articles. After reading the titles and abstracts 52 articles were selected for full-reading. Subsequently, two articles were excluded. In the articles included, 25 anticholinergic activity measuring scales were identified , whose main characteristics are presented in Table 1

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Table 1. Characteristics and frequency of the drugs included in the scales in relation to the 349 drugs identified in the scales analyzed.

Scale name	Country and year	Development process	Drugs included	Percentage
Crideco Anticholinergic Activity Scale – CALS[1]	Espanha, 2022	ARS, ACB, Duran's Scale, CAS, GABS, KABS. Experts' opinion.	204	58.5%
Salahudeen's Scale – SS[20]	Nova Zelândia, 2015	Systematic review on previous scales.	193	55.3%
Anticholinergic Impregnation Scale – AIS[28]	França, 2020	Literature review, previously published scales: ADS, ARS, ACB, ABC, CrAS, AAS, ACL, Durán's scale, Salahudeen's scale and experts' opinion.	179	51.3%
Korean Anticholinergic Burden Scale– KABS[29]	Coreia, 2019	Literature review; Previously published scales: ACB, ADS, ARS, ACL, CrAS, Chew's list, AAS, ABC; 2015 Beers Criteria; and experts' opinion.	158	45.3%
Anticholinergic Drug Scale – ADS[30]	Estados Unidos, 2006	Previously published scales and experts' opinion.	141	40.4%
German Anticholinergic Burden Scale – GABS[31]	Alemanha, 2018	Literature review; Published scales: ADS, ABC, CrAS, AAS, ACB, ACL, ACB, Duran's List; AGS/Beers Criteria 2015; DRUGDEX® and experts' opinion.	137	39.3%
Brazilian Anticholinergic Activity Drug Scale – BADS[7]	Brasil, 2019	Literature review; Published scales: ADS, ABC, CrAS, ARS, Chew's list, ACB, AAS, ACL, AEC, MARANTE and AIS; AGS/ beers Criteria 2015; Martindale® and experts' opinion.	113	32.4%
Chew's list– CHEW[16]	Estados Unidos, 2008	Serum anticholinergic activity.	104	29.8%
Delirogenic Risk Scale – DRS[32]	Alemanha, 2015	German pharmacovigilance group's list, Priscus' and Chew's list.	102	29.2%
Duran Scale – Duran[19]	Equador, 2013	ADS, ABC, CrAS, ARS, Chew's list, AAS and ACL Martindale® scales.	99	28.4%
Drug Delirium Scale – DDS[33]	Canadá, 2017	Literature review; Published scales: ARS, ADS, ACB, Beers criterion and STOPP criterion and experts' opinion.	86	24.6%
Anticholinergic Effect on Cognition – AEC[34]	Reino Unido, 2017	Literature review, muscarinic receptors *in vitro* affinity, dissociation constant (pkI) for cholinergic receptors, ability to cross the blood-brain barrier and reports of adverse effects.	82	23.5%
Anticholinergic Cognitive Burden Scale – ACB[35]	Estados Unidos, 2008	Based on a systematic review, serum anticholinergic activity, *in vitro* affinity for muscarinic receptors and experts' opinion.	80	22.9%
Modified Anticholinergic Cognitive Burden Scale – mACB[36]	Austrália, 2019	Based on previously published scales: ACB and ARS.	78	22.3%
Anticholinergic Loading Scale – ALS[37]	Austrália, 2011	CrAS scale, serum anticholinergic activity and experts' opinion.	76	21.8%
Clinician-rated Anticholinergic Score – CrAS[38]	Estados Unidos, 2008	Based on a previously published scale and on experts' opinions.	60	17.2%
Summer's Class of Drug List – SCDL[15]	Estados Unidos,1978	Clinical study conducted in a hospital.	59	16.9%
Anticholinergic Risk Scale – ARS[39]	Estados Unidos, 2008	Based on a literature review, dissociation constant (pkI) for cholinergic receptor and Micromedex referral for adverse effects.	50	14.3%
Anticholinergic Activity Scale – AAS[17]	Noruega, 2010	Based on the Chew's List scale, serum anticholinergic activity, literature review and experts' opinion.	47	13.5%
Muscarinic Acetylcholinergic Receptor ANTagonist Exposure – MARANTE[10]	Bélgica, 2016	Based on the Duran's List drugs, authoritative sources and experts' opinion.	43	12.3%
Clinical Index and Pharmacological Index – CI-PI[18]	Estados Unidos, 2004	Anticholinergic drug effects, binding to receptors, experts' opinion, literature review and effects of anticholinergic drugs on neurocognitive and neuropsychological function.	28	8.0%
Cancelli's Anticholinergic Burden Scale – CANCEL[40]	Itália, 2008	Based on a previously published scale, serum anticholinergic activity and experts' opinion.	28	8.0%
Anticholinergic Toxicity Score – ATS[21]	Estados Unidos, 2017	Computational model (Morgan algorithm and Tanimoto coefficient).	25	7.2%
Cao's Scale – Cao[41]	Austrália, 2008	Mosby's Drug Consult and Drugs with anticholinergic activity identified by Peters.	24	6.9%
Anticholinergic Burden Classification – ABC[14]	França, 2006	Serum anticholinergic activity, literature review and experts' opinion.	19	5.4%

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The scales were developed in the United States of America, South America (Brazil, Ecuador), Europe (Germany, Belgium, Spain, France, Norway) and Asia (Australia, Korea), showing predominance of the United States and Europe. The most recent scale with the highest number of drugs described is the *Crideco Anticholinergic Activity Scale* (CALS)[1]. The *Anticholinergic Burden Classification*[14] has fewer drugs. The *Summer's Class of Drug List*[15] is the oldest scale.

In relation to the scoring system, most scales use scores from 0 to 3. Scores from 0 to 4 are adopted by CHEW[16] and by the *Anticholinergic Activity Scale* (AAS)[17]. The MARANTE Scale adopts a system that considers the drug dose[10]. The *Clinical Index* (CI) adopts a systematic approach based on equivalence in relation to 1 mg of oral benzatropin mesylate[18]. The Durán scale adopts a high and low anticholinergic potency systematic approach, based on previous scales and on *Martindale's The Complete Drug Reference*[19].

The *Salahudeen* scale uses a method similar to the one employed in Durán's list. A systematic review on anticholinergic activity scales classified anticholinergic activity as low, moderate or high[20].

The ATS scale authors relied on a computational model, the Morgan algorithm, calculating the inhibition capacity of muscarinic receptors using the Tanimoto coefficient, to evaluate the anticholinergic potential of the drugs. The molecular structure was identified in the *Drug Bank Online* and bioactivity in the ChEMBL21 database. ATS grants specific scores for each muscarinic receptor subtype, varying from 0 to 1, where 0 represents that the drug has no known anticholinergic activity or that no interaction was identified through the structure-bioactivity relationship. 1 indicates that the drug has known bioactivity for a specific muscarinic receptor. Scores between 0 and 1 indicate that an interaction has been identified. Finally, the scores corresponding to each receptor subtype are added up to obtain the final value[21].

In the scales, 347 synthetic drugs and two plant extracts (Belladonna and *Scopolia*) were identified. The *Scopolia* extract is obtained from *Scopolia sp* rhizomes, is included in the Japanese Pharmacopoeia and has atropine and scopolamine as active components. The Belladonna Extract, obtained from *Atropa belladonna L.*, has as atropine its major chemical marker, which is a racemic mixture of R-hyoscyamine and S-hyoscyamine. The extracts were considered in this study as natural products, considering the plant type found in the extract, despite having more than one active ingredient in their composition. It is noteworthy that, among the synthetic drugs, we detected hyoscyamine, scopolamine and atropine, active ingredients that are found in the extracts. A total of 349 drugs were considered to be present in the scales.

The following synonyms have been identified but computed as the international common name to avoid duplication of the same drug: Alimemazine/ Trimeprazine; Benzatropine/Benztropine; Chlorphenamine/Chlorpheniramine; Dicyclomine/Dicycloverine; Diphenidramine/Dimenhydrinate; Levomepromazine/ Methotrimeprazine; Meclozine/Meclizine; Meperidine/Petidine; Pyrilamine/ Mepyramine; and Scopolamine/Hyoscine.

Among the 349 drugs with anticholinergic activity classified according to the pharmacological subgroups (Level 3) of the ATC classification, the most frequently listed are shown in Table 2. The most frequent drugs were from subgroups N06A - antidepressants (amitriptyline, imipramine and paroxetine), N05B - anxiolytics (diazepam) and A02B - drugs for peptic ulcer and gastroesophageal reflux disease (ranitidine). Analyzing the pharmacological subgroups, the following were identified as the most prevalent: N06A- antidepressants, N05A- antipsychotics and R06A- antihistamines.

Table 2. Drugs with absolute frequency greater than 15 found in the anticholinergic activity scales.

Fármaco	Nível 3 ATC	N	Fármaco	Nível 3 ATC	N
Amitriptyline	N06A	25	Clozapine	N05A	17
Imipramine	N06A	22	Fentanyl	N02A	17
Diazepam	N05B	21	Fluoxetine	N06A	17
Paroxetine	N06A	21	Orhenadrine	N04A	17
Ranitidine	A02B	21	Perphenazine[1]	N05A	17
Atropine	A03B	20	Theophylline	R03D	17
Chlorpheniramine	R06A	20	Amantadine	N04B	16
Codeine	R05D	20	Cimetidine	A02B	16
Diphenhydramine	R06A	20	Hidroxyzine	N05B	16
Nortriptyline	N06A	20	Loratadine	R06A	16
Olanzapine	N05A	20	Thioridazine	N05A	16
Oxybutynin	G04B	20	Tolterodine	G04B	16
Trihexyphenidyl	N04A	20	Benzatropine[1]	N04A	15
Doxepin[1]	N06A	19	Cetirizine	R06A	15
Haloperidol	N05A	19	Cyiproheptadine	R06A	15
Alprazolam	N05B	18	Clomipramine	N06A	15
Carbamazepine	N03A	18	Digoxin	C01A	15
Loperamide	A07D	18	Fluvoxamine	N06A	15
Promethazine	R06A	18	Mirtazapine	N06A	15
Quetiapine	N05A	18	Morphine	N02A	15
Risperidone	N05A	18	Sertraline	N06A	15
Citalopram	N06A	17	Trazodone	N06A	15
Chlorpromazine	N05A	17			

[1]Drug not registered in Anvisa. N06A – Antidepressants N05B – Anxiolytics ; A02B – Drugs for peptic ulcer and gastro-oesophageal reflux disease ; A03B- Belladonna and derivatives, plain; R06A - Antihistamines for systemic use; R05D-Cough suppressants, excl. Combinations with expectorants; N05A - Antipsychotics; G04B – Urologicals ; N04A - anticolinérgicos; N03A- Anticholinergic agents; A07D- antipropulsives; N02A- Opioids; R03D- Other systemic drugs for obstructive airway diseasesN04B- Dopaminergic agents; C01A- Cardiac glycosides

Amitriptyline was the drug found in all 25 scales identified. Among the drugs present in 15 or more scales, we have the following ones with intrinsic anticholinergic activity: atropine (20), oxybutin (20), orphenadrine (17) and benzatropine (15). Most of the drugs found in the scales had indirect anticholinergic activity.

According to the *Kappa Cohen* statistics, presented in Table 3, the scales with high agreement (>0.60) were ACB x mACB; ADS x BADS; ADS x GABS; ADS x KABS; ADS x SS; BADS x GABS; BADS x mACB; GABS x KABS; GABS x SS and SS x CALS.

Table 3. Agreement levels of the anticholinergic activity scales in relation to the drugs present in them, according to the *Kappa Cohen* statistics.

	AAS	ABC	ACB	ADS	AEC	ALS	ARS	BADS	GABS	KABS	mACB	CrAS	AIS	CIPI	Dur	SS	ATS	MART	CHEW	CAN	CALS	SCDL	Cao	DDS	DRS
AAS																									
ABC	0.21																								
ACB	0.38	0.28																							
ADS	0.37	0.12	0.58																						
AEC	0.41	0.16	0.52	0.53																					
ALS	0.37	0.14	0.26	0.47	0.40																				
ARS	0.25	0.07	0.37	0.36	0.47	0.21																			
BADS	0.35	0.17	0.54	0.68	0.56	0.45	0.40																		
GABS	0.33	0.14	0.42	0.70	0.54	0.54	0.25	0.67																	
KABS	0.24	0.11	0.42	0.68	0.40	0.42	0.24	0.59	0.71																
mACB	0.49	0.22	0.66	0.51	0.60	0.50	0.43	0.62	0.51	0.38															
CrAS	0.28	0.08	0.31	0.33	0.39	0.27	0.33	0.31	0.31	0.26	0.33														
AIS	0.18	0.09	0.24	0.44	0.31	0.35	0.18	0.46	0.56	0.43	0.35	0.19													
CIPI	0.30	0.11	0.29	0.16	0.26	0.06	0.37	0.13	0.10	0.09	0.27	0.26	0.06												
Dur	0.23	0.12	0.54	0.50	0.52	0.19	0.43	0.45	0.34	0.36	0.39	0.43	0.25	0.24											
SS	0.20	0.09	0.38	0.65	0.37	0.32	0.22	0.49	0.62	0.57	0.38	0.29	0.53	0.10	0.47										
ATS	0.17	0.27	0.41	0.20	0.28	0.15	0.37	0.21	0.12	0.15	0.34	0.25	0.06	0.37	0.25	0.12									
MART	0.29	0.20	0.35	0.26	0.40	0.27	0.42	0.36	0.30	0.22	0.40	0.35	0.22	0.27	0.49	0.20	0.26								
CHEW	0.24	-0.01	0.12	0.21	0.26	0.24	0.16	0.18	0.18	0.12	0.22	0.25	0.00	0.10	0.08	0.02	0.13	0.18							
CAN	0.42	0.30	0.24	0.15	0.17	0.15	0.11	0.18	0.15	0.13	0.25	0.16	0.07	0.19	0.11	0.10	0.20	0.20	0.10						
CRID	0.15	0.08	0.29	0.47	0.29	0.28	0.19	0.39	0.51	0.48	0.30	0.19	0.47	0.08	0.37	0.70	0.08	0.17	-0.07	0.08					
SCDL	0.18	0.05	0.21	0.12	0.18	0.02	0.10	0.09	0.04	0.016*	0.14	0.34	-0.03	0.21	0.18	0.04	0.23	0.11	0.01	0.06	0.01				
CAo	0.06	0.18	0.31	0.14	0.22	0.08	0.37	0.12	0.08	0.06	0.23	0.16	0.03	0.17	0.24	0.09	0.36	0.23	0.01	0.04	0.06	0.21			
DDS	0.17	0.15	0.35	0.37	0.37	0.18	0.28	0.32	0.34	0.25	0.30	0.26	0.18	0.14	0.36	0.24	0.20	0.29	0.03	0.16	0.18	0.18	0.14		
DRS	0.28	0.21	0.39	0.38	0.32	0.24	0.17	0.35	0.38	0.28	0.33	0.17	0.17	0.16	0.31	0.25	0.15	0.32	0.15	0.19	0.20	0.12	0.11	0.42	

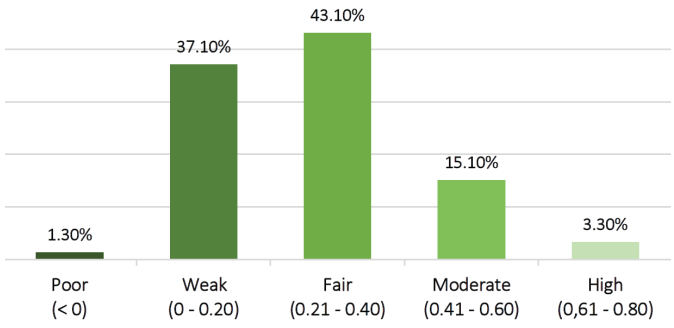
Kappa <0.00 – Poor agreement; from 0.00 to 0.20 – Weak agreement; from 0.21 to 0.40- Fair agreement; from 0.41 to 0.60 – Moderate agreement; from 0.61 to 0.80 – High agreement; and from 0.81 to 1.00 – Almost perfect agreement [13]. AAS: Anticholinergic Activity Scale; ABC: Anticholinergic Burden Classification; ACB: Anticholinergic Cognitive Burden Scale; ADS: Anticholinergic Drug Scale; AEC: Anticholinergic Effect on Cognition; ALS: Anticholinergic Loading Scale; ARS: Anticholinergic Risk Scale; BADS: Brazilian Anticholinergic Activity Drug Scale; GABS: Anticholinergic Burden Scale; KABS: Korean Anticholinergic Burden Scale; mACB: Modified Anticholinergic Cognitive Burden Scale; CrAS: Clinician-rated Anticholinergic Score; AIS: Anticholinergic Impregnation Scale; CIPI: Clinical Index and Pharmacological Index; Dur: Duran's Scale; SS: Salahudeen's Scale; ATS: Anticholinergic Toxicity Score; MART: Muscarinic Acetylcholinergic Receptor ANTagonist Exposure; Chew: Chew's list; CAN: Cancelli's Anticholinergic Burden Scale; CALS: Crideco Anticholinergic Activity Scale; SCDL: Summer's Class of Drug List; Cao: Cao's Scale; DDS: Drug Delirium Scale; DRS: Delirogenic Risk Scale.

The scales that had poor agreement (*Kappa Cohen*'s coefficient <0) were ABC x CHEW, AIS x CHEW, AIS x SCDL, and CHEW x CALS.

Figure 1 shows the scales stratified according to the agreement scale proposed by Landis and Koch (1977). It is evidenced that only 3.3% have a high agreement degree and that the highest proportion has fair (43.1%) and weak (37.1%) agreement levels.

The comparison of the drugs included in the 25 scales studied by the *Kappa Fleiss* statistics showed fair agreement, with an overall *Kappa* coefficient of 0.269, confidence interval (95%) of 0.263 to 0.275, and p-value=0.000.

Figure 1. Agreement analysis according to the *Kappa Cohen* statistics of the drugs included in the anticholinergic activity scales.



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Discussion

This study showed the evolution corresponding to the availability of anticholinergic activity scales for use in the clinical practice of older adults' care and in pharmacoepidemiological research, identifying 25 scales that covered 349 drugs, with predominance of drugs with indirect anticholinergic action. The relevance of identifying drugs with anticholinergic effects is evident, in order to ensure an adequate measurement of the anticholinergic burden. When developing scales, it is also important to ensure the presence of direct-acting anticholinergic drugs in them, which cover anticholinergic drugs contained in ATC Level 4 (A03AA, A03AB, A03BA, A03BB, A03CA, A03CB, A03DA, A03DB, A04AD, G04BD, N04AA, 04AB, N04AC, S01FA, R03BB and R03AL).

The low proportion of drugs found in the scales, considering the 349 identified, reflects the development process of the instruments. Frequently, the scales are developed solely by assessing the drugs that are available in national markets. Currently, the pharmaceutical market displays great dynamism; thus, incorporation of a drug not available at the time the scale was developed can occur in a short period of time after it has been elaborated. In addition to that, by only including drugs registered in the country, international application of the scale is compromised, as well as comparisons between studies[2]. The current trend is to develop scales with an international perspective and covering more drugs, as was the case with CALS[1]. An important strategy to improve the predictive power of anticholinergic action scales is to include in their structure drugs whose antagonistic action on muscarinic receptors has been proved[22].

In 2023, a universal list of drugs with anticholinergic activity was published by Lavrador *et al.*, based on the available documentation regarding the activity of drugs on muscarinic receptors and their ability to cross the blood-brain barrier[22]. The universal list does not present the anticholinergic action scores; therefore, it is not considered a scale. The drugs included in the universal list were identified from 23 scales, all included in this study.

The profile of the drugs included in the scales, with predominance of those that act on the nervous system (Group N- ATC) and on the feeding tract and metabolism (Group A- ATC), is in agreement with a study that analyzed 23 anticholinergic scales[2]. Using the ATC classification and the international common name in developing the scales is important to avoid drugs duplication and to allow comparisons. The inclusion of natural products in the scales must be well specified, informing the plants' name to allow identifying the active ingredients with anticholinergic activity.

Amitriptyline was the only drug present in all 25 scales found, a result that is similar to the one detected in a systematic review that analyzed 11 scales[23]. Amitriptyline is classified as with high anticholinergic activity in all the scales. It is considered a potentially inappropriate drug for older adults[24], of a class commonly prescribed to treat depression, and is available in the basic component in the National List of Essential Medications (*Relação Nacional de Medicamentos Essenciais*, RENAME). It is noteworthy that the fact that a drug is found in fewer scales does not reflect that it does not have anticholinergic activity, as this can be due to being used in fewer countries.

The fair agreement level between the scales reflects their development process focused on experts' opinions, which may use different criteria to classify anticholinergic activity. In addition to that, some scales were based on serum anticholinergic activity, contributing to variation in composition of the scales.

The scales with high agreement levels are the most current and their elaboration process was based on a literature review and on scales already published and validated, such as ACB, ADS and ARS. These factors contribute to higher agreement levels.

BADS shows greater agreement with GABS, KABD and mACB, scales that are more recent and cover more drugs. Development of these scales was based on a literature review and on previous scales, considering the arsenal of drugs available in the countries, reflecting the current pharmacotherapy practice. The moderate agreement of BADS with these international scales shows that it is an adequate Brazilian scale to measure anticholinergic burden.

To increase agreement between the drugs to be included in the anticholinergic activity scales, it is important to incorporate, in the development process, objective information regarding activity of the drugs on the muscarinic receptors available in databases such as the *Drug Bank Online* and *Inxight*[2].

The divergences among the drugs that make up the different scales, as well as among the values attributed to the anticholinergic activity, may come to influence the results corresponding to the prevalence of using anticholinergic drugs and of anticholinergic burden. Epidemiological studies that analyzed these outcomes, incorporating comparative analysis of scales, identified poor agreement between the scales[25,26,27].

The study contributes to the clinical practice by investigating the agreement levels between the anticholinergic activity scales using adequate statistical analysis, but it has limitations. One of them is that it analyzed the scales with a focus on the drugs, without considering the anticholinergic activity scores, a divergence point across several scales. Another limitation is the fact that bibliographic research was only carried out in PubMed/MEDLINE in a non-systematic way. However, the research was able to identify systematic reviews already published on anticholinergic scales, which may have contributed to an adequate identification of the scales already published. Despite this limitation, it was possible to identify a large number of scales available for clinical use and in pharmacoepidemiological research.

Conclusion

The availability of anticholinergic activity scales is increasing, with 25 scales identified. The agreement across all 25 scales identified in relation to the drugs included is fair. For the drugs included in the scales, weak and fair agreement levels were predominant considering the pairs of scales. Moderate agreement between pairs of scales was scarce in number and covered the following scales: ACB, mACB, ADS, BADS, GABS and CALS.

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Collaborators

JSO and AMR participated in preparation of the project, analysis, data interpretation, writing of the article and content review. All authors approved the final version of the article.

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Declaration of conflict of interests

The authors declare that there are no conflicts of interests in relation to this article.

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