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Use of drugs with anticholinergic activity in outpatients with multiple myeloma: associated factors and agreement between measurement scales

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Abstract

Objective: to determine frequency and factors associated with anticholinergic drugs (DAch) use in patients with multiple myeloma (MM) and analyse the agreement between three anticholinergic scales in classification and categorization of anticholinergic burden. **Methods:** it was carried out a cross-sectional study with MM outpatients in different services in a state capital city in Brazil. Anticholinergic activity was identified by Brazilian Anticholinergic Activity Drug Scale (BAADS), Anticholinergic Cognitive Burden Scale (ACB), and Anticholinergic Risk Scale (ARS). Multiple logistic regression was performed to identify associated factors. Agreement between scales in classification and categorization of anticholinergic burden determined by Fleiss Kappa and weighted Kappa, respectively. **Results:** 213 patients with MM were included, median age was 67.2 years. The median number of drugs used was 6 (IQR=6; min=1 and max=19), and approximately 153 (72%) of the patients used polypharmacy. It was identified 56 drugs used with anticholinergic activity. The most used DAch were antidepressants, antipsychotics, and opioids. Frequency of DAch use ranged from 12.7% to 70%. Low agreement was observed in the classification of DAch (k= 0.144). Between BAADS and ACB there is moderate agreement in the classification of cumulative anticholinergic burden (k=0.562; agreement=66.2%). Use of DAch was associated with polypharmacy, according to the three scales. **Conclusion:** Frequency of DAch use was high, according to BAADS and ACB scales, and positively associated with polypharmacy. There is low agreement classification of DAch and moderate agreement in categorization of anticholinergic burden. Future research should investigate the impact of DAch in clinical outcomes, benefits of anticholinergic deprescribing and criteria to determine DAch score.

Keywords: multiple myeloma; cholinergic antagonists; polypharmacy; drug therapy.

Utilização de medicamentos com atividade anticolinérgica em pacientes ambulatoriais com mieloma múltiplo: fatores associados e concordância entre escalas de mensuração

Resumo

Objetivo: determinar a frequência de utilização de MAch e os fatores associados ao seu uso em pacientes com MM. Analisar a concordância entre três escalas de mensuração da atividade anticolinérgica. **Métodos:** Estudo transversal com pacientes com MM atendidos em serviços ambulatoriais de uma capital do sudeste do Brasil. A atividade anticolinérgica foi identificada empregando as escalas: Escala Brasileira de Medicamentos com Atividade Anticolinérgica (EBMAA), Anticholinergic Cognitive Burden Scale (ACB) e Anticholinergic Risk Scale (ARS). Realizou-se a regressão logística múltipla para identificar os fatores associados ao uso de MAch. A concordância entre as escalas na classificação e na categorização da carga anticolinérgica cumulativa foram determinadas pelo Fleiss Kappa e Kappa ponderado, respectivamente. **Resultados:** Foram incluídos 213 pacientes com MM, a mediana da idade foi de 67,2 anos. Os pacientes utilizaram em média seis medicamentos (IQR=6; min=1 and max=19) e 71,8% utilizavam polifarmácia. Identificou-se 56 medicamentos com atividade anticolinérgica, sendo os mais frequentes: antidepressivos, antipsicóticos e opióides. Observou-se baixa concordância entre os escores na classificação dos MAch (k= 0,144). Entre A EBMAA e ACB há concordância moderada na classificação da carga anticolinérgica cumulativa (k= 0,562; concordância= 66,2%). Polifarmácia apresentou associação positiva com uso de medicamento com atividade anticolinérgica segundo as três escalas analisadas. **Conclusão:** A frequência de utilização de

MAch foi elevada nos pacientes com MM, de acordo com a EBMAA e positivamente associada à polifarmácia. Há baixa concordância entre as três escalas na classificação dos MAch e concordância moderada na categorização da carga anticolinérgica cumulativa.

Palavras-chave: mieloma múltiplo; antagonistas colinérgicos; polifarmácia; farmacoterapia

Introduction

Multiple myeloma (MM) is an incurable disease characterized by the proliferation of plasma cells within the bone marrow, the clinical manifestations are due to the physiological changes promoted by accumulation of these malignant plasma cells in the marrow [1]. This disease is generally associated with advanced age and male gender, approximately 33% of patients, at diagnosis, are over 75 years old [1]. In 2020, there were 176,404 new cases of MM in the world, with an incidence of 1.78/100,000 inhabitants [2].

There was an improvement of patient survival in the last 15 years due to the new therapies available for the treatment of MM [1]. The use of polypharmacy is associated with an increased risk of potentially inappropriate prescribing (PIP), and it is frequent in MM patients[4,5]. American Geriatric Society Beers Criteria for Potentially Inappropriate Medication and STOPP/START, consider several anticholinergic drugs (DAch) as potentially inappropriate medication [5,6].

Considering this, it is important to highlight that DAch can induce adverse events related to the blockade of the central and peripheral cholinergic system[7]. Negative clinical outcomes such as cognitive and functional deficits, falls, and hospitalization can be induced by DAch[8]. Classical DAch, such as atropine and oxybutynin, have intrinsic anticholinergic properties and act by blocking acetylcholine receptors in the central and peripheral nervous system. However, there are indirect DAch that are not related to their primary indication, such as some antidepressants and antipsychotics[7].

The intrinsic or indirect anticholinergic activity of multiple drugs used concomitantly defines the cumulative anticholinergic burden of the pharmacotherapy[7,8]. The anticholinergic burden is measured by the sum of the individual anticholinergic activity of the drug, using available scales and lists published[9].

The number of DAch scales and lists available for use in clinical practice and research is increasing. However, there is no definition of a gold standard scale to determine the cumulative anticholinergic burden of pharmacotherapy[9,10].

Cohorts studies have shown that anticholinergic use is common, especially in older adults, and higher anticholinergic burden is associated with poorer physical and cognitive ability, impaired ability to perform activities of daily living, increased risks of falls, dementia and poor quality of life[11-13]. However, investigations on anticholinergic burden including MM patients have not been identified in the literature. Reducing the anticholinergic burden is one of the strategies for optimizing pharmacotherapy and preventing negative outcomes[7-10].

Thus, the main objective of this study was to determine the frequency of use of DAch in patients with MM and factors associated with their use. The secondary objective is to analyse the agreement between three anticholinergic scales in relation to the classification and measurement of anticholinergic burden present in pharmacotherapy.

Methods

Study design, location, and population

This is a cross-sectional study that included outpatients diagnosed with MM, aged 18 years or older, who were able to respond to the interview, and signed the informed consent. This study is part of the research project "Adverse Events, Treatment Adherence, and Quality of Life in Patients with Multiple Myeloma.", which included patients diagnosed with MM who underwent drug treatment in public and private healthcare settings. It was carried out in three different health services in a state capital city in Brazil: i. high complexity public hospital; ii. outpatient oncology and hematology public service; and iii. private oncology and hematology clinic.

The study was conducted by a coordination and a research team without the direct involvement of local researchers at the data collection sites. It was invited to participate of this study all patients identified with diagnostic of MM from the participating centers and who attended appointments during one year, from April 2019 to March 2020. Patients were recruited from a pre-existing scheduling list. The study objectives were explained to each eligible patient, and the informed consent form was presented. Those who agreed to participate voluntarily signed the informed consent. Patients who were in remission period and were not using any other medication were excluded in this study.

The study approved by the Research Ethics Committee of the Federal University of Minas Gerais, number CAAE 05400818.3.0000.5149.

Data Collection

After signing the informed consent form, the participant was invited to answer a questionnaire developed by the researchers as a tool, which comprised sociodemographic, clinical, and medication-related characteristics. Interviews were conducted by trained researchers and electronically recorded using the Questionnaire Development System (QDS), version 2.6.1.1. It was collected at the interview information on the current use of medications. In order to complement the information obtained during the face-to-face interviews, additional data were systematically extracted from the medical records of all participants. For this purpose, a standardized form, specifically developed by the research team, from the medical records were retrieved data on antineoplastics and supportive therapy medications and, also, information related to clinical variables.

Variables

The dependent variable of the study was the use of DAch. Anticholinergic activity was identified using the following scales: the Brazilian Anticholinergic Activity Drugs Scale (BAADS)[14], Anticholinergic Cognitive Burden Scale (ACB)[7], and the Anticholinergic Risk Scale (ARS)[15].

BAADS classifies DAch in scores 1-3 that indicate, respectively, low, moderate and high anticholinergic activity[14]. ACB scale classifies DAch in scores 1-3, with score 1 representing drugs with anticholinergic effects but without relevant negative cognitive effects, and scores 2 and 3 representing drugs with established and clinically relevant anticholinergic effects on cognitive function [7]. ARS scale classifies DAch in scores 0-3, with score 0 - drugs with no or limited anticholinergic potential, score 1 - drugs with moderate anticholinergic potential, score 2 - drugs with strong anticholinergic potential, and score 3 - drugs with very strong anticholinergic potential[15]. The frequency of individuals exposed to DAch and the drugs that contribute to anticholinergic activity were identified according to each scale. The anticholinergic burden obtained according to each scale was categorized as: absent – 0; low - 1 to 2; and high - ≥3. DAch were classified according to the Anatomical Therapeutic Chemical (ATC) classification using levels 1 (anatomical) and 3 (therapeutical).

The independent variables were: i. sociodemographic: age, sex, education, income, health service; ii. clinical variables: history of hospitalization, multimorbidity, diseases, ISS – International Staging System, adverse event reported in medical records; iii. pharmacotherapeutic: polypharmacy (use of five or more drugs, except parenteral antineoplastic drugs).

Data Analysis

For categorical variables descriptive analysis, it was performed using frequencies and proportions, for quantitative variables it was used measures of central tendency and variability. Normal distribution of the data was evaluated by Shapiro Wilk test.

The agreement between the scores of the three scales in the classification of the drug with anticholinergic activity was determined using the Fleiss Kappa statistic.

To verify the agreement between the scales in relation to the cumulative anticholinergic burden in pharmacotherapy (absent, low, and high), the weighted Kappa was calculated[16]. The following interpretation was used for the degree of agreement: <0.00-poor; 0.00 to 0.20-weak; 0.21 to 0.40-regular; 0.41 to 0.60-moderate; 0.61 to 0.80-high; 0.81-1.00 almost perfect[17].

To assess the association between the use of drugs with anticholinergic activity and the independent variables in the univariate analysis it was used Pearson's chi-square test. The analysis was performed, separately, for each of the scales. Participants who used one or more DAch were compared to those who did not use any drugs with this activity. DAch were considered drugs with score ≥ 1 in the investigated scales. It was included in the multivariate logistic regression analysis, those variables with p ≤0.20 in the univariate analysis. Backward stepwise method obtained the final multivariate model, remaining the variables with p-value ≤0.05. Odds Ratio (OR) estimated the strength of the association, with a confidence interval (CI) of 95 %. The fit of the final model of the multiple regression analysis was verified by Hosmer-Lemeshow test. Data were analysed using the Statistical Package for Social Sciences® (SPSS®), version 25.0.

Results

The study included 213 patients with MM, whose median age was 67.2 years (interquartile range IQR=17; min=39 and max=92), 10 were excluded because did not use medications besides antineoplastic. Of 213, 56.8 % were assisted by the private service. In the MM staging criteria, 36,8% were in stage I and 34,7% in stage III.

Most patients 120 (56.3%) had multimorbidity. The most frequent disease was arterial hypertension 133 (62.4%), followed by diabetes mellitus 52 (24.4%). The median number of drugs used was 6 (IQR=6; min=1 and max=19), and approximately 153 (72%) of the patients used polypharmacy. It was identified that 57 (26.8%) patients were on thalidomide-based treatment regimens, 35 (16.4 %) were taking bortezomib, 23 (10.8%) were taking thalidomide+bortezomib, 26 (12.2%) were using other regimens, and 72 (33.8%) were not using anticancer drugs at the time of the interview (Table 1).

We identified 56 drugs used with anticholinergic activity, of which 55 (98.2 %) drugs were listed in the BAADS, 36 (64.3 %) drugs were listed in the ACB, and 16 (28.6 %) drugs were listed in the ARS. Table 2 presents the drugs with anticholinergic activity used by the participants who presented an absolute frequency >2. Dexamethasone, tramadol, codeine, and atenolol were the most frequent drugs. The most used DAch belong mainly to Nervous System according level 1 (anatomical) ATC .These drugs were the following therapeutic groups (level 3) of the ATC classification: antidepressants, antipsychotics, and opioids (Table 2).

The median of anticholinergic burden according to BAADS was 1 (IQR=2 minimum=0 and maximum=8), for ACB it was 0 (IQR=1 minimum=0 and maximum=7), and ARS was 0 (IQR=0 minimum=0 and maximum=7). Low agreement was observed between the scores of the three scales in the classification of the DAch (k= 0.144; 95 % CI 0.086-0.202, p=0.000). However, agreement was moderate when the scales classified the drugs in score 3 (k=0.432; 95 %CI 0.340-0.525; p=0.000) (Table 3).

Agreement was moderate between BAADS and ACB scales in the classification of the anticholinergic burden present in the pharmacotherapy of the participants (k= 0.562; 95 % CI 0.480-0.645; p= 0.000; agreement = 66.2 %); the scales mainly agree with anticholinergic burden for absent (44.7 %) and low (39.7 %). There is low agreement between the ARS scale and the other two scales in the classification of cumulative anticholinergic burden (Table 4).

Univariate analysis showed that the following are associated with the use of DAch: multimorbidity, polypharmacy, hypertension (except according to the ARS scale), depression (except according to the ACB scale), diabetes (only according to the ACB scale), higher education, female, history of hospitalization, and chronic kidney disease (CKD) (only according to the BAADS) (Table 1).

In the final logistic regression model of the multivariate analysis, polypharmacy was positively associated with the use of one or more drugs with anticholinergic activity, according to the three scales analysed. The female gender showed a positive association with the use of DAch only according to the Brazilian scale, depression only according to the ARS scale, and hypertension only according to the ACB scale (Table 5).

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Table 1. Description of MM patients treated at the three outpatient clinics and univariate analysis of sociodemographic, clinical and pharmacotherapeutic variables with the use of drugs with anticholinergic activity according to the scales used (n=213).

		BAADS			ACB			ARS		
	General Description	Use of DAch	Univariate analysis		Use of DAch	Univariate analysis		Use of DAch	Univariate analysis	
Variable	N (%)	N (%)	OR (CI 95%)	*p	N (%)	OR (CI 95%)	p*	N (%)	OR (CI 95%)	p*
Sociodemographic										
Sex										
Female	111 (52.1)	89 (80.2)	2.83 (1.54-5.22)	0.001	58 (52.3)	1.44 (0.84-2.48)	0.183	15 (13.5)	1.17 (0.52-2.64)	0.702
Male	102 (47.9)	60 (58.8)	1		44 (43.1)	1		12 (11.8)	1	
Income**										
≤3 minimum salaries	98 (46.0)	70 (78.4)	1.14 (0.63-2.95)	0.665	51 (52.0)	1.36 (0.79-2.34)	0.263	15 (15.3)	1.55 (0.69-3.49)	0.287
>3 minimum salaries	115 (54.0)	79 (68.7)	1		51 (44.3)	1		12 (10.4)	1	
Schooling										
Never studied + elementary school	98 (46.0)	73 (74.5)	1.50 (0.83-2.72)	0.182	48 (49.0)	1.08 (0.63-1.86)	0.768	14 (14.2)	1.31 (0.58-2.93)	0.515
High school + higher education	115 (54.0)	76 (66.1)	1		54 (47.0)	1		13 (11.3)	1	
Age										
≥ 60 years	155 (72.8)	108 (69.7)	0.95 (0.49-1.85)	0.886	77 (49.7)	1.30 (0.71-2.39)	0.393	20 (12.9)	1.08 (0.43-2.71)	0.871
< 60 years	58 (27.2)	41 (70.7)	1		25 (43.1)	1		7 (12.1)	1	
Service										
Public	92 (43.2)	66 (71.7)	1.16 (0.64-2.10)	0.620	45 (48.9)	1.07 (0.62-1.85)	0.794	14 (15.2)	1.49 (0.66-3.35)	0.331
Private	121 (53.8)	83 (68.6)	1		57 (47.1)	1		13 (10.7)	1	
Clinical										
Hospitalization history										
Yes	57 (26.8)	42 (73.7)	1.28 (0.65-2.53)	0.047	24 (42.1)	0.73 (0.39-1.34)	0.307	5 (8.8)	0.58 (0.21-1.63)	0.301
No	156 (73.2)	107 (68.6)	1		78 (50.0)	1		22 (14.1)	1	
Multimorbidity										
Yes	120 (56.3)	93 (77.5)	2.28 (1.25-4.13)	0.006	66 (55)	1.93 (1.12-3.36)	0.018	19 (15.8)	1.99 (0.83-4.79)	0.116
No	93 (43.7)	56 (60.2)	1		36 (38.7)	1		8 (8.6)	1	
SAH										
Yes	133 (62.4)	102 (76.7)	2.31 (1.27-4.21)	0.006	76 (57.1)	2.77 (1.55-4.95)	0.000	19 (14.3)	1.50 (0.62-3.61)	0.363
No	80 (37.6)	47 (58.8)	1		26 (32.5)	1		8 (10.0)	1	
CKD										
Yes	31 (14.5)	25 (80.6)	1.95 (0.76-5.01)	0.160	17 (54.8)	1.38 (0.645-2.98)	0.402	4 (12.9)	1.02 (0.33-3.19)	0.967
No	182 (85.5)	124 (68.1)	1		85 (46.7)	1		23 (12.6)	1	
Depression										
Yes	11 (5.2)	10 (90.9)	4.53 (0.57-36.2)	0.179	6 (54.5)	1.32 (0.39-4.48)	0.650	4 (36.4)	4.45 (1.21-16.36)	0.015
No	202 (94.8)	139 (68.8)	1		96 (47.5)	1		23 (11.4)	1	
Diabetes										
Yes	52 (24.4)	39 (75.0)	1.391 (0.68-2.83)	0.361	29 (55.8)	1.52 (0.81-2.85)	0.191	7 (13.5)	1.09 (0.43-2.76)	0.845
No	161 (75.6)	110 (68.3)	1		73 (45.3)	1		20 (12.4)	1	
Pharmacotherapeutic										
Adverse events										
Yes	192 (90.1)	134 (69.8)	1.28 (0.41-4.00)	0.765	91 (47.4)	0.90 (0.304-2.667)	0.851	24 (12.5)	1.86 (0.23-12.84)	0.553
No	14 (9.9)	9 (64.3)	1		7 (50.0)	1		1 (7.1)	1	
Polypharmacy										
Yes	153 (71.8)	125 (86)	8.66 (4.46-16.82)	0.000	87 (56.90)	3.95(2.03-7.70)	0.000	26 (17.0)	12.08(1.60-91-14)	0.002
No	60 (28.2)	24 (40.0)	1		15(25.0)	1		1 (1.7)	1	

*Pearson's chi-square test. **1 minimum salarie= 228,93 dollars (exchange rate: December/2022)
SAH-Systemic Arterial Hypertension; CKD- Chronic Kidney Disease; OR-Odds ratio; CI- Confidence interval; MM- Multiple Myeloma; ACB- Anticholinergic Cognitive Burden Scale; BAADS- Brazilian Anticholinergic Activity Drug Scale; ARS- Anticholinergic Risk Scale.

Table 2. Anticholinergic drugs with a frequency greater than 2, stratified by scale.

ATC Classification	Drug	Frequency N (%)	Scales		
ATC Level *			BAADS	ACB	ARS
A-Alimentary Tract and Metabolism		9 (3.4)			
A02B Drugs for peptic ulcer and gastroesophageal reflux disease	Ranitidine	3	X	X	X
A03F Propulsives	Metoclopramide	4	X		X
A03F Propulsives	Domperidone	2	X		
B -Blood and Blood Forming Organs		7 (2.7)			
B01A Antithrombotic	Warfarin	7	X	X	
C-Cardiovascular System		59 (22.4)			
C01D Vasodilators	Isosorbide	3	X	X	
C02D Arteriolar vasodilator	Hydralazine	2	X	X	
C03B Thiazide diuretics	Chlorthalidone	4	X	X	
C03C Loop Diuretics	Furosemide	14	X	X	
C07A Beta Blockers	Atenolol	18	X	X	
C07A Beta Blockers	Metoprolol	16	X	X	
C08D Non-dihydropyridine calcium channel blockers	Diltiazem	2	X		
H- Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins		62 (23.6)			
H02A Corticosteroids for systemic use	Dexamethasone	54	X		
H02A Corticosteroids for systemic use	Prednisone	8	X	X	
M- Musculo-Skeletal System		5 (1.9)			
M03B Centrally acting muscle relaxants	Cyclobenzaprine	3	X	X	X
M04A Anti-hyperuricemic	Colchicine	2	X	X	
N -Nervous System		101 (38.4)			
N02A Opioids	Tramadol	20	X		
N02A Opioids	Morphine	10	X	X	
N02A Opioids	Oxycodone	2	X		
N03A Antiepileptics	Clonazepam	13	X		
N03A Antiepileptic	Phenobarbital	2	X		
N05A Antipsychotic	Haloperidol	2	X	X	X
N05A Antipsychotics	Quetiapine	5	X	X	X
N05A Antipsychotics	Chlorpromazine	2	X	X	X
N05B Anxiolytics	Alprazolam	10	X	X	
N06A Antidepressants	Escitalopram	9	X		
N06A Antidepressants	Citalopram	8	X		
N06A Antidepressants	Fluoxetine	6	X		
N06A Antidepressants	Amitriptyline	3	X	X	X
N06A Antidepressants	Mirtazapine	3	X		X
N06A Antidepressants	Sertraline	2	X		
N06A Antidepressants	Venlafaxine	2	X	X	
N07B Drugs used in addictive disorders	Methadone	5	X		
R- Respiratory System		20 (7.6)			
R05D Antitussives**	Codeine	20	X	X	

*The first letter denotes the first level of the ATC classification; **Pure codeine, used as an analgesic, is classified in this group. ATC-Anatomical Therapeutic Chemical.

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Table 3. Agreement between the scales in the classification of anticholinergic drugs.

General Kappa(CI 95%)	Score	Fleiss Kappa(CI 95%)	P-value
0.144 (0.086-0.202)*	0	-0.102 (-0.914--0.010)	0.030
	1	0.147 (0.055-0.240)	0.002
	2	0.242 (0.150-0.334)	0.000
	3	0.432 (0.340-0.525)	0.000
*P-value = 0.000			

Table 4. Agreement between the scales in the classification of the individuals' anticholinergic burden.

Scales	Weighted Kappa(CI 95%)	P-value	Agreement (%)	
BR X ACB	0.562 (0.480-0.645)	0.000	Absent	63 (44.7)
			Low	56 (39.7)
			High	22 (15.6)
			Total	141 (66.2)
BR X ARS	0.152 (0.091-0.214)	0.000	Absent	64 (84.2)
			Low	4 (5.3)
			High	8 (10.5)
			Total	76 (35.7)
ACB X ARS	0.152 (0.091-0.214)	0.000	Absent	109 (86.5)
			Low	10 (8.0)
			High	7 (5.5)
			Total	126 (59.2)

Discussion

To the best of the authors' knowledge, the present study is the first to investigate the use of DAch by patients with MM. The study identified that the use of DAch was positively associated with polypharmacy, considering the three scales used. Depression was independently associated with the use of DAch according to the ARS scale, female gender was associated according to the Brazilian scale, and hypertension according to the ACB scale. BAADS and ACB scales identified high frequency of DAch use.

MM primarily affects older adults, the median age at diagnosis is approximately 70 years, with 35%-40% affected after 75 years[1]. The frequency of DAch in the present study can be explained by the multimorbidity and polypharmacy. Multimorbidity is common among older MM patients, for this reason many patients concomitantly take multiple medications, including Ach drugs. The use of DAch by cancer patients is not well studied[18], despite their association with adverse events[13,19]. One study found higher anticholinergic burden for the group of elderly patients without cancer diagnosis[18]. In contrast, research with palliative care patients identified that drugs used for symptom management is an important contributing factor to the anticholinergic burden of cancer patients, mainly opioids against refractory pain[20,26]. Dexamethasone, codeine, and tramadol were frequently identified in this study. Dexamethasone is in first-line treatment in MM protocol, which is worth noting, combined with other therapies, and also in regimens for treating relapses[1].

Given the prevalence of cancer among older adults, it is crucial to understand the potential effects of the anticholinergic burden for rational drug use and cancer management. Besides the anty-myeloma therapies, often the MM patients use medication to treat bone disease, kill pain, antimicrobial agents and other supportive drugs. Thus, the supportive therapy prescribed to manage or prevent adverse events related to antineoplastic drugs, increases the treatment burden. So, MM patients might be exposed a high number of drugs during the phases of treatment, explaining the polypharmacy.

The association with polypharmacy identified in this investigation was also detected in other studies and is a known risk factor for the use of DAch, commonly associated with high anticholinergic burden, especially in patients with advanced chronic diseases and elderly cancer patients, due to the presence of multimorbidities[21,22].

Cancer patients are five times more likely to have depression at diagnosis, and patients with hematological malignancies are particularly vulnerable to mental health issues[23], which reflects on quality of life. As it is an incurable disease, MM can further exacerbate levels of depression and anxiety[23], favoring the prescription of antidepressants and anxiolytics. Antidepressants are among the most used DAch in this study, which explains the independent association with depression, according to the ARS scale.

In addition, opioids, antidepressants, and diuretics are among the DAch most frequently used by patients with MM in this study. These drugs are also classified as FRIDS- fall-risk-increasing-drugs. In this context, falls are one of the main adverse events associated with the use of DAch [13,19]. Besides that, bone loss, pain, functional decline, and peripheral neuropathy are prevalent in MM patients and may be associated with an increased risk of falls and fractures[9].

Considering this, the pharmacotherapy review would be a strategy to ensure that polypharmacy comprises only drugs that are appropriate for the health condition and safe for the patient[23,24]. In an institutionalized elderly population, deprescribing resulted in a reduction in participants' anticholinergic burden, number of falls, adverse drug reactions, and frailty scores six months after deprescribing[25].

Table 5. Odds Ratio (OR) estimate via multivariate logistic regression of factors associated with the use of drugs with anticholinergic activity in patients with multiple myeloma treated at the three outpatient clinics.

	BAADS		ACB		ARS	
Variable	OR (CI 95%)	p*	OR (CI 95%)	p**	OR (CI 95%)	p***
Women	3.55 (1.77-7.13)	0.000	-	-	-	-
Polypharmacy	7.87 (3.87-16.00)	0.000	3.24(1.62-6.44)	0.001	12.69 (1.65-97.12)	0.006
Depression	-		-	-	5.00(1.23-20.34)	0.014
Hypertension	-		2.152(1.17-3.96)	0.014	-	-

Hosmer-Lemeshow Quality of Fit Test: (*) Chi-square= 0.784; degrees of freedom= 2; p=0.676, (**) Chi-square=0.398 degrees of freedom=2; p=0.819 (***) Chi-square=4.604 degrees of freedom=2; p=0.100.

Regarding cancer patients, the relationship of cancer treatment, polypharmacy and the fragility of the patient must be considered.

BAADS is composed of a greater number of DAch than the other two scales, as a result, a higher frequency of DAch use was detected in patients with MM. Therefore, the differences in the frequencies of use of DAch according to the three scales can be attributed to their structure. Only 13 drugs identified are simultaneously present in the three scales; dexamethasone and tramadol are included only in the BAADS and represent most of the DAch prescriptions in this study, which justifies the higher prevalence according to this scale. In Colombia, a similar situation was reported with tramadol in the comparison of three scales for the assessment of DAch in elderly patients with fractures[27].

The low agreement between ARS and ACB has been previously described[27,28]. The following factors contribute to the low agreement: specificities of the scale development methods, differences in the validation process, variability in the number of drugs included in each scale, and systematic definition of the of anticholinergic activity weight magnitude[28]. BAADS reflects the usual prescription pattern once the study was carried out in the same country where the scale was developed.

Despite the general agreement of the scales, there is moderate agreement among the three scales in assigning a score of 3 for anticholinergic activity. Score of 3 is generally assigned to a drug that has well-defined anticholinergic activity and is clearly associated with adverse events[7,14,15]. There are more divergences in the criteria adopted in the classification of the lowest value scores [7,14,15].

An immense variability of drugs that make up each scale is evident, as well as in the anticholinergic activity weight for each drug. In this context, it is challenging to use the existing scales in clinical practice and also in the measurement of exposure to DAch in pharmacoepidemiological research. It is essential to improve the validation process and development of scales to measure anticholinergic activity, although many validation studies are of good quality and with an impressive sample size, many of them are cross-sectional studies, which is not good to assess adverse drug effects[29,30].

Besides that, these scales and indexes are very useful, once clinicians may use them as a guide to identify drugs with anticholinergic activity, quantify anticholinergic burden, and recognise anticholinergic adverse effects[29].

The present study brings important contributions to the profile of DAch use MM patients, including analysing younger age groups that are commonly understudied. In addition, the profile of use of these drugs was analysed in terms of comparison between international scales and a national scale, allowing a broad reflection on the anticholinergic burden measurement tools available in the literature.

However, the study has limitations because it was analysed a single region of Brazil, which makes it difficult to generalize the results. Due to the design of the study and the availability of information in medical records, it was not possible to access other chronic health conditions and self-medications, which is important, considering that many drugs with significant anticholinergic activity are commonly used as self-medication. There is no information about which patients were in palliative care, which is relevant since they are more likely to be prescribed some DAch. The use of DAch may be underestimated by the self-report of patients and the missing information in the medical records.

The study, by expanding knowledge about the use of DAch in patients with MM, can contribute to optimizing care, especially from the perspective of treatment safety, considering the multimorbidity among patients with MM. In addition, it reinforces the need for further studies to understand factors associated with anticholinergic burden in MM.

Conclusion

The frequency of DAch use was high in the study, according to the BAADS and ACB scales, and was positively associated with polypharmacy, female gender, depression and hypertension. There is low agreement between the three scales in the classification of DAch and moderate agreement in the categorization of cumulative anticholinergic burden. Future research to fill knowledge gaps, encompass developing longitudinal study to identify the impact of anticholinergic burden in clinical outcomes and safety of drug therapy of MM patients, determining the benefits and safety of anticholinergic deprescribing and defining criteria to determine the score for anticholinergic activity of drugs. Better concordance among scales will improve the measurement of DAch use.

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Declaration of interest

The authors declare that there are no conflicts of interest.

Authors' contributions

MSRL, CAMP, PLMD, AMMR, and RMMS contributed substantially to the conception and design of the work. MSRL, LPS, JSM, PLMD, NLC, TRLM contributed substantially to the data collection. MSRL, CAMP, and AMMR performed the analysis and interpretation of data. All the authors contributed substantially to the draft of the manuscript. The final version of the manuscript was approved by all the authors.

References

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548-567. doi:10.1002/ajh.25791
2. Huang J, Chan SC, Lok V, et al. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. Lancet Haematol. 2022;9(9):e670-e677. doi:10.1016/S2352-3026(22)00165-X
3. Umýt EG, Baysal M, Bas V, et al. Polypharmacy and potentially inappropriate medication use in older patients with multiple myeloma, related to fall risk and autonomous neuropathy. J Oncol Pharm Pract. 2020;26(1):43-50. doi:10.1177/1078155219835303

4. Wildes TM, Tuchman SA, Klepin HD, et al. Geriatric Assessment in Older Adults with Multiple Myeloma. J Am Geriatr Soc. 2019;67(5):987-991. doi:10.1111/jgs.15715

5. American Geriatrics Society. American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023;71(7):2052-2081. doi:10.1111/jgs.18372

6. O'Mahony D, Cherubini A, Guiteras AR, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med. 2023;14(4):625-632. doi:10.1007/s41999-023-00777-y

7. Boustani M, Campbell N, Munger S, *et al*. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health*, 2008;**4**(3):311-320. doi:10.2217/1745509X.4.3.311

8. Fox C, Smith T, Maidment I, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. Age Ageing. 2014;43(5):604-615. doi:10.1093/ageing/afu096

9. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. Eur J Clin Pharmacol. 2013;69(7):1485-1496. doi:10.1007/s00228-013-1499-3

10. Lavrador M, Castel-Branco MM, Cabral AC, et al. Association between anticholinergic burden and anticholinergic adverse outcomes in the elderly: Pharmacological basis of their predictive value for adverse outcomes. Pharmacol Res. 2021;163:105306. doi:10.1016/j.phrs.2020.105306

11. Roitto HM, Aalto UL, Öhman H, et al. Association of medication use with falls and mortality among long-term care residents: a longitudinal cohort study. BMC Geriatr. 2023;23(1):375. doi:10.1186/s12877-023-04096-6

12. Norling AM, Bennett A, Crowe M, et al. Longitudinal associations of anticholinergic medications on cognition and possible mitigating role of physical activity. J Am Geriatr Soc. 2023;71(6):1937-1943. doi:10.1111/jgs.18279

13. Stewart C, Yrjana K, Kishor M, et al. Anticholinergic Burden Measures Predict Older People's Physical Function and Quality of Life: A Systematic Review. J Am Med Dir Assoc. 2021;22(1):56-64. doi:10.1016/j.jamda.2020.05.065

14. Nery RT, Reis AMM. Development of a Brazilian anticholinergic activity drug scale. Einstein (Sao Paulo). 2019;17(2):eAO4435. doi:10.31744/einstein_journal/2019AO4435

15. Rudolph JL, Salow MJ, Angelini MC, et al. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168(5):508-513. doi:10.1001/archinternmed.2007.106

16. Gisev N, Bell JS, Chen TF. Interrater agreement and interrater reliability: key concepts, approaches, and applications. Res Social Adm Pharm. 2013;9(3):330-338. doi:10.1016/j.sapharm.2012.04.004

17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-174.

18. Yasin AI, Topcu A, Akuc MN, et al. A comparison of anticholinergic burden in older patients with and without cancer. Future Oncol. 2021;17(36):5067-5075. doi:10.2217/fon-2021-0469

19. Xu XJ, Tan MP. Anticholinergics and falls in older adults. Expert Rev Clin Pharmacol. 2022;15(3):285-294. doi:10.1080/17512433.2022.2070474

20. Hochman MJ, Kamal AH, Wolf SP, et al. Anticholinergic Drug Burden in Noncancer Versus Cancer Patients Near the End of Life. J Pain Symptom Manage. 2016;52(5):737-743.e3. doi:10.1016/j.jpainsymman.2016.03.020

21. Jun K, Ah YM, Hwang S, et al. Prevalence of anticholinergic burden and risk factors amongst the older population: analysis of insurance claims data of Korean patients. Int J Clin Pharm. 2020;42(2):453-461. doi:10.1007/s11096-020-01010-7

22. Feng X, Higa GM, Safarudin F, et al. Prevalence and factors associated with potentially inappropriate medication use in older medicare beneficiaries with cancer. Res Social Adm Pharm. 2020;16(10):1459-1471. doi:10.1016/j.sapharm.2019.12.018

23. Kuczmarski TM, Jaung T, Mancuso CE, et al. Precancer and cancer-associated depression and anxiety among older adults with blood cancers in the United States. Blood Adv. 2022;6(4):1126-1136. doi:10.1182/bloodadvances.2021005862

24. Kantilal K, Kantilal K, Nightingale G, et al. How-to guide for medication reviews in older adults with cancer: A Young International Society of Geriatric Oncology and Nursing & Allied Health Interest Group initiative. J Geriatr Oncol. 2022;13(8):1283-1286. doi:10.1016/j.jgo.2022.05.012

25. Ailabouni N, Mangin D, Nishtala PS. DEFEAT-polypharmacy: deprescribing anticholinergic and sedative medicines feasibility trial in residential aged care facilities. Int J Clin Pharm. 2019;41(1):167-178. doi:10.1007/s11096-019-00784-9

26. Geyer HL, Gazelka H, Mesa R. How I treat pain in hematologic malignancies safely with opioid therapy. Blood. 2020;135(26):2354-2364. doi:10.1182/blood.2019003116

27. Valladales-Restrepo LF, Duran-Lengua M, Castro-Osorio EE, et al. Consistency between anticholinergic burden scales in the elderly with fractures. PLoS One. 2020;15(2):e0228532. doi:10.1371/journal.pone.0228532

28. Naples JG, Marcum ZA, Perera S, et al. Concordance Between Anticholinergic Burden Scales. J Am Geriatr Soc. 2015;63(10):2120-2124. doi:10.1111/jgs.13647

29. Lavrador M. Quantificação da carga anticolinérgica como preditor de resultados clínicos negativos no idoso–um contributo para a prática clínica. Coimbra: Universidade de Coimbra;2021.

30. Lisibach A, Benelli V, Ceppi MG, et al. Quality of anticholinergic burden scales and their impact on clinical outcomes: a systematic review. Eur J Clin Pharmacol. 2021;77(2):147-162. doi:10.1007/s00228-020-02994-x