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Polypharmacy and anticholinergic burden scales in older adults: a cross-sectional study among psychiatric outpatients in a tertiary care hospital

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Abstract

Introduction Mental disorders are prevalent among older adults, often leading to the use of multiple medications, many with anticholinergic properties. Polypharmacy, common in this population, is a major contributor to anticholinergic burden, which is linked to cognitive and physical decline. This study investigates the relationship between polypharmacy and anticholinergic burden across seven anticholinergic burden scales in elderly patients attending the psychiatric outpatient.

Methods Study was conducted at a psychiatry outpatient clinic at All India Institute of Medical Sciences, Rishikesh, India, from December 2021 to March 2023. Elderly patients (aged ≥ 60 years) who were on at least one psychotropic medication and had a primary working diagnosis of psychiatric illness were included. All psychotropic medications, including antidepressants, antipsychotics, mood stabilizers, and hypnotics, were evaluated. Anticholinergic burden scales were calculated by the respective tools. Univariate analysis was adopted to determine the factors that may affect polypharmacy.

Results Study included 1165 elderly patients aged ≥ 60 years. The prevalence of polypharmacy was 20.43% ($n = 238$). Clonazepam ($n = 364$, 17.28%), escitalopram ($n = 197$, 9.35%), metformin ($n = 165$, 7.83%), sertraline ($n = 141$, 6.69%), mirtazapine ($n = 129$, 6.12%), and lorazepam ($n = 110$, 5.22%) were among the most frequently prescribed anticholinergic drugs. Univariate analysis demonstrated that all anticholinergic risk assessment scales were closely correlated with polypharmacy, with the strongest association observed for the Anticholinergic Load Scale (ALS) (Odds Ratio = 4.3; $p < 0.001$). Polypharmacy was also positively associated with adverse drug reactions (Odds Ratio = 1.81; 95% Confidence Interval = 1.27–2.56).

Conclusion The anticholinergic burden in this cohort of elderly psychiatry patients was high, with 95.1% ($n = 1108$) experiencing a significant burden. Adverse drug events and anticholinergic burden scales were positively associated with polypharmacy, with a stronger correlation between polypharmacy and ALS scores than with other anticholinergic burden scales in older adults.

Keywords Anticholinergic burden, Polypharmacy, Elderly, Psychotropics

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Introduction

Mental disorders, defined as disturbances in cognition, emotional regulation, or behaviour, are prevalent among older adults aged 60 and above, with an estimated global prevalence of 21.4% according to the Global Burden of Disease Study 2019 [1]. These disorders often lead to significant distress or functional impairment, impacting major life domains.

Anticholinergic drugs have been in use for treating Parkinson's disease, psychotic disorders, depression, overactive bladder, asthma, allergies and mydriasis. Many psychotropic medications, including antipsychotics, antidepressants, mood stabilizers, and anxiolytics, also exhibit anticholinergic effects to varying degrees. Cognitive decline in older adults without dementia is typically attributed to age-related changes in the central nervous system, but a portion of this decline may be due to the anticholinergic effect of medications [2–4].

The concept of anticholinergic burden refers to the cumulative anticholinergic impact resulting from the use of multiple medications [2]. Over 600 medications possess some level of anticholinergic activity, with a wide range of therapeutic application and adverse effect profiles [5]. Among adults aged 60 and older, 20–40% are reported to be consuming more than five prescription drugs simultaneously, a condition known as polypharmacy [6–8]. Notably, drugs with anticholinergic and sedative properties are particularly common in patients with polypharmacy [9–12], and even medications with low anticholinergic effects can cumulatively contribute to the overall anticholinergic burden. Anticholinergic burden is a strong predictor of cognitive and physical impairment in elderly population and linked to increased rate of falls, cognitive decline, impaired memory,disturbances in daily living and increased mortality [2, 13–15].

Several scales have been developed to assess the anticholinergic burden, each with unique methodologies and focus areas. Methodologies for developing scales vary considerably. Where some are designed to measure both central and peripheral anticholinergic effects, others focus on serum radioreceptor anticholinergic activity assay or muscarinic receptor affinity measurements and may only capture peripheral anticholinergic effects. The Anticholinergic Cognitive Burden (ACB) Scale, developed by Boustani et al. in 2008 [16], is one of the most widely used tools. It assigns scores based on in vitro affinity for muscarinic receptors and clinical evidence of cognitive impairment, particularly focusing on the relationship between anticholinergic use and cognitive decline, such as delirium. Similarly, the Anticholinergic Risk Scale (ARS), introduced by Rudolph et al. in 2008 [17], categorizes drugs based on their anticholinergic potential through a consensus methodology involving expert review. The Anticholinergic Drug Scale (ADS), developed by Carnahan et al. in 2002 [18], evaluates medications based on serum anticholinergic activity (SAA), integrating pharmacological data with clinical outcomes to provide an objective measure of anticholinergic exposure.

The Clinician-Rated Anticholinergic Scale (CrAS), introduced by Han et al. in 2008 [19], relies on clinical consensus to rate medications. The CrAS has been validated against other scales and is predictive of cognitive impairment, making it a robust tool in clinical settings for evaluating anticholinergic burden. The Anticholinergic Load Scale (ALS), developed by Sittironnarit et al. in 2011 [20], incorporates methods from CrAS, ARS, and anticholinergic burden classification [4], assigning scores based on a combination of SAA. This scale is particularly relevant in cases of polypharmacy, commonly seen in older adults.

More recent developments include the Anticholinergic Effect on Cognition (AEC) Scale by Bishara et al. in 2017 [3], which incorporates binding affinities, blood–brain barrier (BBB) penetration, and clinical reports of cognitive impairment. This scale offers a nuanced approach by adjusting scores based on the degree of BBB penetration, providing a refined measure of the drug's impact on cognition. The CRIDECO Anticholinergic Load Scale, introduced by Ramos et al. in 2022 [21], provides an updated approach to assessing anticholinergic burden, particularly within the Spanish population. It integrates previous scales and adapts them to the local pharmacopeia, employing a committee-based approach for uncertain drug classifications.

Despite the availability of various methods to assess anticholinergic burden, there is ongoing debate regarding which measurement provides the most accurate and clinically useful prognostic information [14]. Significant variation exists among these scales due to differences in their development, drug selection criteria, and methods for evaluating anticholinergic potency. Comparative studies on these scales are limited, often showing low to moderate concordance, and they have rarely explored the direct association between polypharmacy and cumulative anticholinergic effects [22, 23]. Understanding this association is crucial for optimizing the management of elderly patients' prescriptions, especially given the complexities introduced by polypharmacy. With multiple anticholinergic burden scales available, it is imperative to determine which is most clinically beneficial and which most closely correlates with polypharmacy. Additionally, we aim to test the hypothesis that older adults with polypharmacy have an elevated anticholinergic burden, associated with greater cognitive and functional impairment.

Methods

This was a cross-sectional study conducted at the psychiatry outpatient department of the All-India Institute of Medical Sciences (AIIMS), Rishikesh, Uttarakhand, India, from December 29, 2021, to March 2023. Patient recruitment followed a consecutive sampling method, with the inclusion criteria specifying that participants must be (a) 60 years of age or older and (b) prescribed at least one psychotropic medication. Although different age cutoffs are noted in the literature, ranging from 60, 65, and 75 years, this study selected the age threshold of 60 years in accordance with the National Elderly Policy in India, which defines elderly individuals as those aged 60 years or above [24, 25]. The study design adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, with a detailed flow chart of the methodology provided in Fig. 1.

Ethical considerations

The study was conducted following approval from the Institutional Ethics Committee (IEC) of AIIMS, Rishikesh (Reference No. 467/IEC/PGM/2021, dated 26/11/2021). Ethical principles in accordance with the Declaration of Helsinki were strictly followed throughout the study.

Measures

Elderly patients aged 60 or older who were prescribed at least one psychotropic medication, categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System, were included in the study. Demographic and anthropometric data were collected through structured interviews conducted by a psychiatrist (VR) and the principal investigator (MB and BD). Diagnoses were made by a psychiatrist according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems, Clinical Modification (ICD-10-CM), established by the World Health Organization (WHO).

Polypharmacy

Polypharmacy was defined as the concurrent use of five or more prescription drugs, a widely accepted and evidence-based threshold in the literature [26]. In our study, patients were classified as experiencing polypharmacy based on the number of medications prescribed at their visit. For the purposes of this study, dietary supplements, herbal medicines, teas, extracts, and ophthalmic topical products were excluded from the polypharmacy calculation.

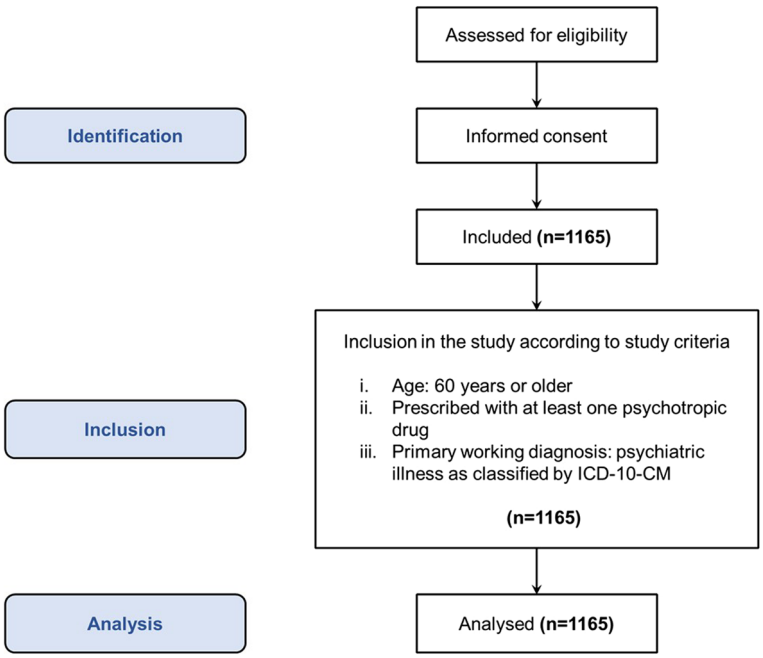

Fig. 1 STROBE flow chart. STROBE, Strengthening the Reporting of Observational Studies in Epidemiology. The STROBE flow chart details the study selection process for patients visiting the psychiatric outpatient. Patients visiting the psychiatric outpatient were assessed for eligibility to be included in the study. Informed consent was obtained. A total of 1165 patients were recruited and analysed at the end of the study duration. Abbreviation: ICD-10-CM 10th revision of the International Statistical Classification of Diseases and Related Health Problems

Anticholinergic scales

All drugs administered to the patients were evaluated using seven anticholinergic burden scales. These scales categorize drugs based on their potential to induce anticholinergic effects, typically ranging from no known anticholinergic activity (score = 0) to high/definite anticholinergic activity (score = 3) [3, 16–21]. The anticholinergic scales utilized were ACB [16], ARS [17], ADS [18], ALS [20], CrAS [19], AEC [3], and CRIDECO scale [21] (Appendix Table F). For each scale, the cumulative anticholinergic effect was determined by summing the scores of all administered drugs. Patients were then divided into two groups according to their total score: those with anticholinergic exposure (score ≥ 1) and those without exposure (score = 0), on any of the scales.

Adverse drug reaction (ADR)

Adverse events were documented for participants aged 60 and older who were exposed to at least one psychotropic medication. A total of 191 ADR reports were recorded using the ADR reporting form from the Central Drugs Standard Control Organisation (CDSCO), Government of India.

Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the psychiatric older adults in the study. Categorical variables were presented as numbers and percentages, while continuous variables were reported as means (M) with standard deviations (SD). Associations between polypharmacy and anticholinergic scale scores were evaluated using univariate analysis, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (Version 25; IBM Corporation, Armonk, NY, USA), and graphical repres entations were created using Microsoft Excel Version 2019 (Microsoft Corporation, Redmond, WA, USA).

Results

A total of 1,165 patients aged ≥ 60 years were assessed in the study, with 56.74% ($n = 661$) men and 43.26% ($n = 504$) women. The mean age was 64.16 (± 5.23) years. Major depressive disorder was the most prevalent disorder, affecting 22.15% ($n = 258$) of the participants, followed by anxiety disorders at 18.11% ($n = 211$) and mood disorders at 14.76% ($n = 172$). Schizophrenia and dementia accounted for 9.96% ($n = 116$) and 7% ($n = 83$), respectively (Table 1).

The average number of medications taken daily by the participants was 3.16 (range = 1–16) per older adult. Polypharmacy, defined as the concurrent use of five or more medications observed in 20.43% of the population ($n = 238$). The average number of CNS-active drugs per prescription was 1.86, with 58.81% ($n = 685$) of participants receiving more than one CNS-active drug, and 1.63% ($n = 19$) meeting the criteria for psychotropic polypharmacy (≥ 5 CNS-active drugs) (Table 1).

The highest level of total polypharmacy was found in the 75 + age group ($n = 34/73$, 46.6%). A sex-related difference was observed in all age groups, with men generally having higher levels of polypharmacy than women. Notably, in the 70–74 age group, 33.3% ($n = 20/60$) of men were exposed to polypharmacy compared to only 9.8% ($n = 4/41$) of women. The difference was also significant in the 75 + age group, where 51.1% ($n = 24/47$) of men were exposed to PP compared to 38.5% ($n = 10/26$) of women. In the 65–69 age group, however, women exhibited higher exposure levels ($n = 32/88$, 36.4%) compared to men ($n = 27/102$, 26.5%), marking an exception to the general trend of male dominance in polypharmacy exposure across the age groups (Fig. 2).

Anticholinergic burden and polypharmacy

Clonazepam ($n = 364$, 17.28%), escitalopram ($n = 197$, 9.35%), metformin ($n = 165$, 7.83%), sertraline ($n = 141$, 6.69%), mirtazapine ($n = 129$, 6.12%), and lorazepam ($n = 110$, 5.22%) were among the most frequently prescribed anticholinergic drugs, each receiving a score of ≥ 1 on at least one of the seven scales. Eighteen drugs had maximum score on either of the scales, with quetiapine ($n = 100$, 4.7%), olanzapine ($n = 88$, 4.18%), amitriptyline ($n = 69$, 3.27%), trihexyphenidyl ($n = 51$, 2.42%), and paroxetine ($n = 40$, 1.9%) being the most common (Fig. 3).

The scores from the anticholinergic burden scales were analysed to determine their association with polypharmacy (Table 2 & Fig. 4). ALS had the highest odds ratio (OR = 4.30) with a highly significant p-value of less than 0.001, indicating that each unit increase in the ALS score increased the risk of polypharmacy by 4.30 times. The CRIDECO (OR = 3.55) and ACB (OR = 3.22) scales also showed moderate associations, while the ADS scale did not show a significant relationship with polypharmacy (OR = 1.14, $p = 0.43$) (Fig. 4 and Appendix Table C). Polypharmacy was also positively associated with adverse drug reactions (OR = 1.81, CI = 1.27–2.56), with common adverse events including sleep disturbances, tremors, and decreased appetite. Clonazepam, escitalopram, and amitriptyline were frequently implicated in these events (Appendix Table E).

Approximately 15% ($n = 169$) of patients were prescribed four medications, and since there was only a minor difference between this group and those with polypharmacy, we conducted an analysis to correlate their anticholinergic burden. Similar to the polypharmacy

Table 1 Demographic, disease and treatment variables ($n = 1165$)

Variable	Grouping	Frequency		
		Male (%)	Female (%)	Total (%)
Age (years)	60–64	452 (56.43)	349 (43.58)	801 (68.76)
	65–69	102 (53.69)	88 (46.32)	190 (16.31)
	70–74	60 (59.41)	41 (40.6)	101 (8.67)
	75 +	47 (64.39)	26 (35.62)	73 (6.27)
Mean Age (SD)		64.27 (5.3)	64.02 (5.12)	64.16 (5.23)
Diagnosis	Major depressive disorder	144 (55.82)	114 (44.19)	258 (22.15)
	Anxiety	108 (51.19)	103 (48.82)	211 (18.11)
	Mood disorder	106 (61.63)	66 (38.38)	172 (14.76)
	Schizophrenia	66 (56.9)	50 (43.11)	116 (9.96)
	Dementia	52 (62.66)	31 (37.35)	83 (7.12)
	Substance use disorder	26 (89.66)	3 (10.35)	29 (2.49)
	Obsessive–compulsive disorder	12 (60)	8 (40)	20 (1.72)
	Stress and adjustment disorders	4 (36.37)	7 (63.64)	11 (0.94)
	Intellectual disabilities	(0)	1 (100)	1 (0.09)
	Other disorders	143 (54.17)	121 (45.84)	264 (22.66)
Comorbidities	Diabetes	101 (58.73)	71 (41.28)	172 (14.76)
	Hypertension	235 (56.91)	178 (43.1)	413 (35.45)
	Hypothyroidism	24 (34.29)	46 (65.72)	70 (6.01)
	Hyperthyroidism	3 (37.5)	5 (62.5)	8 (0.69)
	Cardiovascular diseases	24 (66.67)	12 (33.34)	36 (3.09)
	Cerebrovascular disease	6 (40)	9 (60)	15 (1.29)
	COPD	16 (94.12)	1 (5.89)	17 (1.46)
Number of drugs	Average N (range)	3.19 (1–12)	3.11 (1–16)	3.16 (1–16)
	Polypharmacy (5–16)	140 (58.83)	98 (41.18)	238 (20.43)
	No polypharmacy (1–4)	521 (56.21)	406 (43.8)	927 (79.57)
	1	80 (38.28)	129 (61.73)	209 (17.94)
	2	149 (47.01)	168 (53)	317 (27.21)
	3	103 (44.4)	129 (55.61)	232 (19.91)
	4	74 (43.79)	95 (56.22)	169 (14.51)
	5	48 (43.25)	63 (56.76)	111 (9.53)
	6	28 (45.17)	34 (54.84)	62 (5.32)
	7	11 (44)	14 (56)	25 (2.15)
	8	7 (35)	13 (65)	20 (1.72)
	9	2 (25)	6 (75)	8 (0.69)
	10	1 (25)	3 (75)	4 (0.34)
	11	0 (0)	6 (100)	6 (0.52)
	12	0 (0)	1 (100)	1 (0.09)
	16	1 (100)	0 (0)	1 (0.09)
Number of CNS-active drugs	Average N (range)	1.86 (1–7)	1.85 (1–5)	1.86 (1–7)
	1	279 (58.13)	201 (41.88)	480 (41.2)
	2	241 (54.41)	202 (45.6)	443 (38.03)
	3	91 (55.49)	73 (44.52)	164 (14.08)
	4	37 (62.72)	22 (37.29)	59 (5.06)
	5	11 (64.71)	6 (35.3)	17 (1.46)
	6	1 (100)	0 (0)	1 (0.09)
	7	1 (100)	0 (0)	1 (0.09)
ADR (= 191)	Polypharmacy	35 (62.5)	21 (37.5)	56 (23.5[a])
	No polypharmacy	68 (50.38)	67 (49.63)	135 (14.6[b])

SD Standard Deviation, *CNS* Central Nervous System

[a] proportion of polypharmacy patients having ADR

[b] proportion of non-polypharmacy patients having ADR

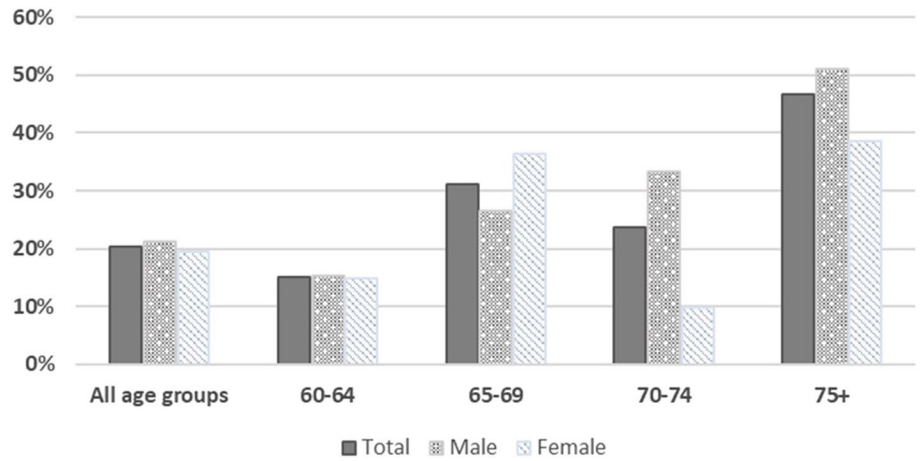

Fig. 2 Prevalence of polypharmacy across different age groups stratified by gender ($n=1165$) Prevalence of polypharmacy across different age groups stratified by gender. The bar chart represents the percentage of individuals using polypharmacy (defined as the concurrent use of five or more medications) across various age groups: 60–64, 65–69, 70–74, and 75 + years. The chart compares total prevalence (solid bars) with male (dashed bars) and female (dotted bars) subgroups. The highest prevalence of polypharmacy is observed in the 75 + age group, particularly among females. In all age groups, females tend to exhibit a higher prevalence of polypharmacy than males. The overall trend shows increasing polypharmacy with advancing age

group, patients on four medications exhibited higher anticholinergic burden scores compared to those on fewer medications. Notably, ACB scores (OR = 4.5, CI = 1.39–14.54) and CRIDECO scores (OR = 3.91, CI = 1.2–12.68) demonstrated a stronger association with the prescription of four medications compared to other scales. Gender and adverse drug reactions (ADR) were not found to be associated with the prescription of four medications (Appendix Figure A and Table D).

Discussion

In this cross-sectional study, anticholinergic burden and polypharmacy were investigated in patients attending the psychiatry outpatient. We observed one-fifth of our study population taking five or more medications with an average of 3.16 drugs prescribed per patient, and on further analysis the polypharmacy and the seven anticholinergic burden scales were found to be positively associated.

Regarding drug use, 20.43% ($n=238$) of the study population used at least five different therapeutic substances daily, a figure that increased with age—rising from 15.1% ($n=121/801$) in individuals aged 60–64 to 46.6% ($n=34/73$) in those aged 75 and above. This aligns with previous studies, though variations exist. For instance, a study conducted in a tertiary care hospital within a similar region reported a much higher polypharmacy prevalence of 93.1% among individuals aged 60 and above [27]. Another cross-sectional study conducted in the psychiatric outpatient department in India, involving 832 elderly patients (≥ 60 years), found that 54.33% of patients were prescribed multiple medications, indicating a high prevalence of polypharmacy [28]. Similarly, Nitya and their colleagues in their cross sectional study conducted in geariatric health clinic documented, usage of average of 4.02 drugs per prescription with 31% of them prescribed with more than five drugs [29]. A systematic review found that the overall prevalence of polypharmacy among older adults in India is approximately 49%, with hyperpolypharmacy (≥ 10 medications) at 31% [30]. An umbrella review analysing eleven meta-analyses incorporating 295 studies and 59,552,762 participants from 41 countries across six continents reported the global prevalence in elderly patients to be 37% [31].

It is imperative to understand that the prevalence of polypharmacy is not a constant parameter, but rather a dynamic one, influenced by various factors such as differences in disease burden, age groups, medication utilization trends, prescriber's discretion, healthcare providers' awareness, patients' education & level of knowledge, study settings, adopted methodologies etc.

Present study identified a sex-based difference in polypharmacy, with men generally exhibiting higher rates of exposure compared to women (21.2% vs. 19.4%), particularly in the 70–74 and 75 + age groups. This could be attributed to higher comorbidity rates in men, such as hypertension (56.91% in men vs. 43.1% in women) and diabetes (58.73% in men vs. 41.28% in women). Interestingly, women aged 65–69 exhibited higher polypharmacy rates than men (36.4% vs. 26.5%), potentially due to factors like underlying illness requiring more medications,

Drugs with score of ≥1 in any of the 7 scales	Frequency (%)	ACB	ARS	CALS	ADS	AEC	ALS	CrAS	Max
Clonazepam	364 (17.28)	1	0	1	1	0	1	0	1
Escitalopram	197 (9.35)	1	0	1	0	0	1	0	1
Metformin	165 (7.83)	1	0	1	0	0	1	0	1
Sertraline	141 (6.69)	1	0	1	1	1	0	1	1
Mirtazapine	129 (6.12)	1	2	1	0	1	0	0	2
Lorazepam	110 (5.22)	1	0	1	1	0	0	0	1
Risperidone	109 (5.17)	1	2	1	0	0	1	1	2
Quetiapine	100 (4.75)	3	2	2	0	2	0	2	3
Olanzapine	88 (4.18)	3	2	2	1	2	0	1	3
Fluoxetine	70 (3.32)	1	0	1	1	1	1	1	1
Amitriptyline	69 (3.27)	3	3	3	3	3	3	3	3
Valproic acid	64 (3.04)	1	0	1	1	0	0	0	1
Aripiprazole	54 (2.56)	1	0	1	0	1	0	0	1
Trihexyphenidyl	51 (2.42)	3	0	3	3	3	0	3	3
Lithium	50 (2.37)	1	0	1	0	1	1	0	1
Paroxetine	40 (1.9)	3	2	2	1	2	2	2	3
Atenolol	25 (1.19)	1	0	1	0	0	0	1	1
Venlafaxine	24 (1.14)	1	0	1	0	0	1	1	1
Dosulepin	19 (0.9)	0	0	2	0	0	0	0	2
Metoprolol	19 (0.9)	1	0	1	0	0	0	1	1
Alprazolam	17 (0.81)	1	0	1	1	0	1	1	1
Chlordiazepoxide	17 (0.81)	1	0	1	1	0	0	1	1
Haloperidol	17 (0.81)	2	1	1	0	0	2	0	2
Amisulpride	15 (0.71)	0	0	1	0	0	0	0	1
Bupropion	15 (0.71)	1	0	1	0	0	0	1	1
Chlortalidone	13 (0.62)	1	0	1	1	0	0	0	1
Domperidone	11 (0.52)	1	0	1	0	1	1	0	1
Promethazine	10 (0.47)	3	2	3	3	3	0	0	3
Nortriptyline	9 (0.43)	3	3	3	3	3	0	3	3
Tiotropium bromide	9 (0.43)	1	0	1	0	0	0	0	1
Clozapine	7 (0.33)	3	3	3	3	3	0	0	3
Diazepam	6 (0.28)	1	0	1	1	1	1	1	1
Hydroxyzine	6 (0.28)	3	2	3	3	1	0	0	3
Imipramine	6 (0.28)	3	3	3	3	3	3	3	3
Levodopa and decarboxylase inhibitor	6 (0.28)	1	1	1	0	0	0	1	1
Tramadol	5 (0.24)	2	0	2	1	0	2	2	2
Trifluoperazine	5 (0.24)	3	3	3	1	2	0	0	3
Cyproheptadine	4 (0.19)	3	2	3	2	3	3	0	3
Metoclopramide	4 (0.19)	1	2	1	0	0	1	0	2
Fluvoxamine	3 (0.14)	1	0	1	1	0	1	0	1
Furosemide	3 (0.14)	1	0	1	1	0	0	0	1
Tizanidine	3 (0.14)	3	2	3	0	0	0	0	3
Chlorpromazine	2 (0.09)	3	3	3	3	3	0	3	3
Cinnarizine	2 (0.09)	0	0	1	0	0	0	0	1
Clomipramine	2 (0.09)	3	0	3	3	3	0	0	3
Dicycloverine	2 (0.09)	3	2	3	3	2	0	0	3
Diltiazem	2 (0.09)	1	0	1	1	0	0	0	1
Glycopyrronium bromide	2 (0.09)	1	0	1	0	0	0	0	1
Oxcarbazepine	2 (0.09)	2	0	2	2	0	0	0	2
Prochlorperazine	2 (0.09)	0	2	2	1	2	2	2	2
Zuclopenthixol decanoate	2 (0.09)	0	0	2	0	0	0	0	2
Baclofen	1 (0.05)	1	1	2	0	0	0	2	2
Carbamazepine	1 (0.05)	2	0	2	2	1	0	1	2
Flupentixol	1 (0.05)	0	0	1	0	0	0	0	1
Fluphenazine	1 (0.05)	1	3	2	1	1	3	0	3
Loperamide	1 (0.05)	2	1	1	1	0	1	1	2
Methotrexate	1 (0.05)	1	0	1	0	0	1	0	1
Opipramol	1 (0.05)	2	0	3	0	0	0	0	3
Paliperidone	1 (0.05)	1	0	1	0	0	0	0	1
Piperacillin and beta-lactamase inhibitor	1 (0.05)	1	0	1	1	0	0	0	1
Prednisolone	1 (0.05)	1	0	1	1	1	0	0	1

Fig. 3 Frequency and Maximum Scores for Anticholinergic Drugs across Seven Anticholinergic Burden Scales. Frequency and Maximum Scores for Anticholinergic Drugs across Seven Anticholinergic Burden Scales. This figure presents the anticholinergic burden scores assigned to various drugs based on seven different scales, which are highlighted using yellow and pink shading. Yellow represents lower anticholinergic burden scores (1 or 2), while pink indicates higher anticholinergic burden scores (3). Each row corresponds to a specific drug, and the columns list the anticholinergic scores from each scale. The drugs are organized to display their variability in scoring across scales, highlighting differences in how each scale evaluates anticholinergic burden. Drugs with a score of 3 (high anticholinergic effect) on multiple scales are shaded in pink, indicating stronger anticholinergic potential according to those scales. This visualization helps to contrast the scoring systems and identify discrepancies in drug classification across the scales. Abbreviations: *ACB* Anticholinergic Cognitive Burden, *ARS*: Anticholinergic Risk Scale, *ADS* Anticholinergic Drug Scale, *ALS*: Anticholinergic Load Scale, *CrAS* Clinician-rated Anticholinergic Scale, *AEC* Anticholinergic Effect on Cognition, *CALS* CRIDECO Anticholinergic Load Scale

Table 2 Distribution of scores of the anticholinergic burden scales in polypharmacy and non-polypharmacy population

Scale	Polypharmacy Mean (range)	No Polypharmacy Mean (range)
ACB score	3.6 (0–10)	2.21 (0–9)
ARS score	1.4 (0–6)	1.06 (0–6)
CRIDECO (CALS)	3.4 (0–9)	2.06 (0–9)
ADS score	1.58 (0–6)	1.17 (0–6)
AEC score	1.55 (0–6)	1.14 (0–8)
ALS score	1.78 (0–7)	1.04 (0–6)
CrAS score	1.55 (0–7)	0.95 (0–6)

ACB Anticholinergic Cognitive Burden, *ARS* Anticholinergic Risk Scale, *ADS* Anticholinergic Drug Scale, *ALS* Anticholinergic Load Scale, *CrAS* Clinician-rated Anticholinergic Scale, *AEC* Anticholinergic Effect on Cognition, *CALS* CRIDECO Anticholinergic Load Scale, *SD* Standard Deviation

prescriber discretion, and the higher incidence of diabetes (26.14% vs. 20.6% in men) and thyroid disorders (7.96% vs. 0% in men) in this age group (Table A).

Our study revealed a relatively moderate rate of CNS-active drugs prescriptions among elderly patients receiving psychiatric care, with an average of 1.86 (range = 1–7) CNS-active psychotropic medications per patient. Antidepressants were the preferred choice across all diagnostic categories, except for patients diagnosed with psychosis, schizophrenia, and dementia. Notably, Clonazepam ($n=364$, 17.28%), benzodiazepine, prescriptions were prevalent in our population. Most common illnesses were major depressive disorder (22.15%) and anxiety disorders (18.11%), and benzodiazepine group drugs continue to be the prescriber's preference. In patients with major depressive disorder, anxiety is often a co-occurring condition and clonazepam is frequently prescribed to manage these anxiety symptoms. This might be the factor in prevalent prescription of clonazepam.

Wang and colleagues, found that the prevalence of benzodiazepine use in Chinese patients with major depressive disorder was notably high at 42.9% with oxazepam as most prefered choice, indicating regional variations in benzodiazepine preference [32].

Regarding the use of anticholinergic drugs, in our sample drugs marked anticholinergic effects that are clinically relevant to cognition include antidepressants (amitriptyline, nortriptyline, imipramine, paroxetine), antipsychotics (olanzapine, quetiapine,trihexyphenidyl),

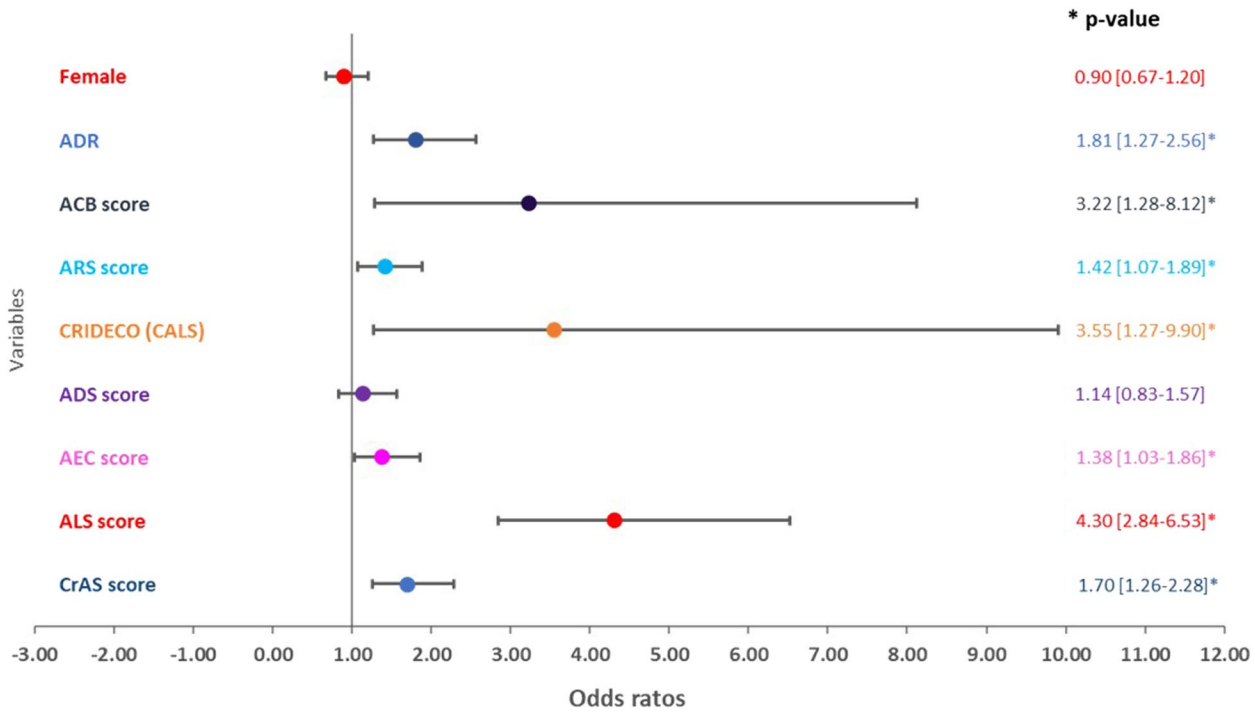

Fig. 4 The odds ratios of polypharmacy according to the anticholinergic burden scales and other variables. Odds Ratios for Polypharmacy vs Various Variables. This plot displays ORs and 95% Cis for different variables influencing polypharmacy in older psychiatric outpatients. Key findings include significant associations with adverse drug reactions (OR = 1.81), presence of antipsychotics (OR = 1.64), and various anticholinergic burden scores. The ALS score shows the strongest association with polypharmacy (OR = 4.30). The x-axis represents odds ratios, indicating the impact strength of each variable on polypharmacy likelihood, with values over 1 indicating increased likelihood. Abbreviations: *ACB* Anticholinergic Cognitive Burden, *ARS*: Anticholinergic Risk Scale, *ADS* Anticholinergic Drug Scale, *ALS*: Anticholinergic Load Scale, *CrAS* Clinician-rated Anticholinergic Scale, *AEC* Anticholinergic Effect on Cognition, *CALS* CRIDECO Anticholinergic Load Scale

and antihistaminics (promethazine, hydroxyzine, cyproheptadine) whereas drugs with moderate antihcolinergic effects include antidepressant and antianxiety drugs (clonazepam, lorazepam, escitalopram, sertraline, fluoxertne).

A retrospective cross-sectional study conducted in Slovenia evaluated the anticholinergic burden in the general population and found that the proportion of patients exposed to anticholinergic burden was highest among older adults (43.2%), followed by adults (25.8%) and children (20.7%) [33]. This highlights that anticholinergic burden is more prevalent in the elderly population.

Similarly in our study nearly all elderly patients ($n=1108$, 95.1%) were prescribed at least one drug with an anticholinergic burden score of ≥ 1 on any of the scales used. All scales, except for ADS (OR = 1.14, CI = 0.83–1.57), showed a statistically significant association with polypharmacy, consistent with previous research linking higher anticholinergic scores to increased medication use [34, 35].

Among the seven scales, the ALS scale exhibited the strongest relationship with polypharmacy (OR = 4.3). However, the CRIDECO and ACB scales identified a larger number of anticholinergic drugs within the study population (61 and 55 drugs, respectively), compared to the ALS scale, which identified only 22 drugs (Appendix Table B and Table F). The observed disparities in odds ratios could be due to the fact that the CRIDECO and ACB scales identified anticholinergic drugs even among non-polypharmacy patients, potentially reducing their specificity in relation to the polypharmacy group (Table 2).

The CRIDECO and ACB scores showed a moderate relationship with polypharmacy (with ORs of 3.55 and 3.22, respectively). ARS, AEC, and CrAS showed a weaker association with polypharmacy (ORs ranging from 1.38 to 1.7), while ADS exhibited the least association (OR = 1.14). These differences likely reflect variations in the drugs included in each anticholinergic scale [23].

Interestingly, nortriptyline and chlorpromazine had the highest anticholinergic burden scores (=3) on all scales except for the ALS scale, which did not include these drugs. The ACB scale identified 16 drugs with maximum anticholinergic activity, followed by CRIDECO with 14. These discrepancies may explain the varied associations of the scales with polypharmacy (Appendix Table B).

Hwang et al. validated the Korean Anticholinergic Burden Scale (KABS) and found it more predictive than ACB, ARS, and ADS for anticholinergic-related emergency visits, showing significant variations in identifying high-risk patients [36].

Soysal et al. compared three anticholinergic risk scales (ADS, ACB, and Duran) and found significant associations between higher anticholinergic burden and both cognitive and physical decline in older adults [37].

These variations highlight existence of variations among anticholinergic measurement scales and the importance of selecting scales tailored to specific populations for accurate risk assessment.

Polypharmacy is a known risk factor for ADRs, with literature showing that the risk of ADRs rising from 13% with two medications to 58% with five drugs, and up to 82% with seven or more drugs [38]. In our study, 23.5% ($n=56/238$) of elderly patients with polypharmacy experienced adverse events, compared to 14.6% ($n=135/927$) in the non-polypharmacy group (Table E). Univariate analysis confirmed that polypharmacy was associated with a significantly higher risk of ADRs (OR = 1.81, CI = 1.27–2.56), with common ADRs including sleep disturbances, tremors, and decreased appetite. Clonazepam, escitalopram, and amitriptyline were frequently implicated in these events. (Appendix Table E).

In further analysis, we observed that patients prescribed four medications, though not strictly classified as polypharmacy, displayed a significant anticholinergic burden. Specifically, the Anticholinergic Cognitive Burden (ACB) scale and the CRIDECO scale showed stronger associations in this subgroup, with odds ratios of 4.5 and 3.91, respectively, highlighting a heightened anticholinergic load even at this threshold. This finding suggests that the potential impact on cognitive and physical health may begin to emerge at medication counts below traditional polypharmacy definitions. Our results align with emerging evidence that moderate polypharmacy (fewer than five medications) can still contribute substantially to anticholinergic load and related adverse outcomes, emphasizing the importance of careful prescribing practices even for those not meeting full polypharmacy criteria [15, 39].

The use of multiple low-risk drugs can lead to clinically significant anticholinergic burden [40]. Therefore, polypharmacy is an important risk for anticholinergic burden. In our study, 20.4% of the patients experienced polypharmacy, and a significant relationship was observed between the extent of polypharmacy and elevated anticholinergic burden. Moreover, while the use of drugs with high anticholinergic scores significantly contributed to the burden, the concomitant use of medications with lower anticholinergic scores also played a crucial role.

Given the established risks of anticholinergic medications in older adults, as outlined by criteria such as STOPP-START, Beers, EU-7, and PRISCUS, reducing anticholinergic burden is a key intervention to mitigate cognitive decline [2, 13, 41–43]. Our study's positive association between polypharmacy and anticholinergic burden suggests that polypharmacy could serve as a

proxy for anticholinergic load, offering a potential target for deprescribing efforts.

The strengths of the present study include its large sample size, offering a solid foundation for statistical analysis and ensuring reliable findings. Additionally, the study provides a comprehensive evaluation of anticholinergic burden across seven different scales, making it one of the few studies to assess polypharmacy and anticholinergic burden with such breadth. This multi-scale approach adds depth to the understanding of how these scales compare in measuring anticholinergic effects, particularly in elderly patients.

However, the study also has limitations. The single-center design may reduce the generalizability of the findings to other populations or settings. As an observational study, it is also subject to potential confounding factors that could influence the results. Moreover, the cross-sectional nature of the study limits the ability to assess long-term clinical outcomes associated with anticholinergic burden and polypharmacy, which could provide a more comprehensive understanding of the risks and consequences involved.

We also acknowledge the heterogeneity of the sample as a limitation of the study. The study population included patients with varying clinical conditions and comorbidities, which may have influenced the results. This heterogeneity could impact the strength and generalizability of the findings.

Conclusions

In this study, we observed a significant association between polypharmacy and anticholinergic burden across seven different scales, reinforcing the complexity of managing medication use in elderly patients attending psychiatry outpatient. The findings underscore the widespread prescription of drugs with anticholinergic properties, contributing to cognitive and physical impairment risks in this vulnerable population. While most anticholinergic burden scales demonstrated a positive relationship with polypharmacy, variations in drug identification and odds ratios among the scales highlight the need for careful selection of the most appropriate tool for clinical evaluation. Future research should investigate whether deprescribing based on polypharmacy measures differs in clinical outcomes from interventions guided by specific anticholinergic scales.

Abbreviations

ACB	Anticholinergic Cognitive Burden
ARS	Anticholinergic Risk Scale
ADS	Anticholinergic Drug Scale
ALS	Anticholinergic Load Scale
CrAS	Clinician-rated Anticholinergic Scale
AEC	Anticholinergic Effect on Cognition
CALS	CRIDECO Anticholinergic Load Scale

Supplementary Information

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Additional file 1: Appendix Figure A. Anticholinergic burden risk with respect to being prescribed with four medications (vs less than four medications). Appendix Table A. Distribution of comorbidities age and gender-wise. Appendix Table B. Number of drugs identified each scale in the present study. Appendix Table C. The relationship between anticholinergic burden scales and polypharmacy (≥5 medications). Appendix Table D. The relationship between anticholinergic burden scales and patients having four medications vs less than four medications. Appendix Table E. Distribution of reported adverse events with causal drugs. Appendix Table F. Distribution of drugs with anticholinergic property across the scales in our study.

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Authors' contributions

MB: conception and design, acquisition of data, performed statistical analysis and interpretation of data, drafting of the manuscript. BD: conception and design, review and substantial edits to the manuscript. VR and SM: curated data, reviewed and edited the final draft., HS, AA, MG, and FA: data analysis and revision of manuscript.

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Data availability

The data in this study are available upon written request to the corresponding author.

Declarations

Ethics approval and consent to participate

Ethical approval for this study protocol was obtained from the Institutional Ethics Committee (IEC) (Reference No. 467/IEC/PGM/2021, dated 26/11/2021), AIIMS, Rishikesh. Written informed consent was obtained from all participants after a detailed explanation of the study prior to its commencement.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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