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Evaluation of Psychotropic Drug Interactions and Inappropriate Use in Older Adults: A Cross-sectional Study

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ABSTRACT

Objectives: Polypharmacy is common in older patients, and psychotropic medications prescribed to treat psychiatric disorders are an important cause of it. This study aimed to find out the potential drug–drug interactions that can happen when older outpatients take psychotropic medications along with other medications and to assess the changes in the anticholinergic burden (ACB) score.

Methods: This cross-sectional study was conducted in a community pharmacy between January 30 and March 30, 2024. Older patients who visited the pharmacy between these dates, had at least one psychotropic medication in their prescription, and had been using at least one medication for the last month were included in this study. The Lexicomp® database was used to determine the interactions of psychotropics, the 2023 Beers Criteria® were used to evaluate medication suitability, and the ACB Calculator® was used for the ACB score.

Results: The sample received 278 psychotropic medications on 211 prescriptions, and the most commonly prescribed was escitalopram. A total of 815 medication interactions were detected, 10 of which were at the X level and 88 at the D level. When psychotropics prescribed to older adults were evaluated according to the 2023 Beers criteria®, 16 different psychotropics prescribed were found to be potentially inappropriate according to 166 criteria. The ACB scores of the patients increased significantly after a psychotropic medication prescription ($p<0.001$).

Conclusion: Given the high frequency of interactions and the increased ACB caused by psychotropic medications, it is important to evaluate their prescription for older patients with geriatric criteria. The results of the present study led us to suggest that all physicians should consider other medications and geriatric criteria when prescribing psychotropic medication to older patients.

Keywords: Anticholinergic burden score, Beers criteria®, Drug interactions, Older patients, Psychotropic medication

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INTRODUCTION

More than 80% of older adults experience neuropsychiatric disorders.[1] While some conditions have only a low presentation, for instance, the Centers for Disease Control and Prevention estimates that the prevalence of major depressive disorder in older adults varies between 1% and 5%; these rates increase with comorbidities or according to health care. These neuropsychiatric disorders often require psychotropic medication for management. Psychotropic medications include antipsychotics, antidepressants, and anticholinergic medications with psychotropic side effects. The use of psychotropic medications increases with age.[2-4]

Pharmacokinetic changes, such as changes in the absorption, distribution, and clearance of medication, and pharmacodynamic changes, such as changes in the response to the medication, are observed with the aging process. Due to these physiological changes, older adults are the most sensitive patient group to drug interactions.[5]

The use of psychotropic medications on their own or in combination with other medications may lead to unexpected drug interactions and adverse reactions. It is known that more than 30% of adverse reactions are caused by drug interactions, leading to significant morbidity each year. In a study in the literature, it was shown that 47.6% of the potential drug–drug interactions (pDDIs) detected in patients were psychotropic drug interactions. Although the number of potential psychotropic drug interactions did not differ significantly between older and younger adults, it was higher in older patients. Most studies in the literature focus on pDDIs between psychotropic medications prescribed to inpatients. However, data on pDDIs between psychotropic medications prescribed in outpatient settings and other previously regularly used medications are scarce.[6-10]

Increased health costs because of adverse drug reactions resulting from potentially inappropriate medication (PIM) use constitute an important public health problem. PIM use in older adults increases morbidity and mortality rates.[11-13] Researchers developed criteria such as Beers, START/STOPP, and TIME-to-START/TIME-to-STOPP to evaluate drug use in older adults. These criteria should be used to determine the appropriateness of medication use in older adults.

The prevalence of potentially inappropriate psychotropic (PIP) use in older adults is reported to be approximately 30%, and almost half of the patients receiving psychotropics have used at least one PIP. The *Beers criteria*® include additional caveats regarding the use of psychotropic medications in older adults, and prescriptions for older adults taking psychotropic medications should be screened against the *Beers criteria*®. Psychotropic medications continue to be prescribed for a wide range of medical conditions despite some evidence of their efficacy and side effects in geriatric adults. Such behavior raises concerns about the inappropriate prescribing of psychotropics. Few studies have evaluated the prevalence of PIM in older adults.[14,15]

Psychotropic medications cause an increase in anticholinergic burden (ACB). Consequently, using potentially inappropriate medications (PIPs) in older adults has been linked to a higher occurrence of side effects, including loss of psychomotor function, cognitive function decline, and falls.[16-18]

To ensure the appropriate use of psychotropic medications in older patients, it is important to consider the demographic characteristics, medications, drug interactions, and ACB scores of the patients and to evaluate them with geriatric criteria.[19]

This study aimed to identify pDDIs that may occur when older outpatients take psychotropic medications in combination with other medications, to evaluate changes in the ACB score, and to determine whether pharmacists are using psychotropic medications appropriately.

METHOD

This cross-sectional study was conducted in a community pharmacy in Trabzon, Turkey. Between January 30 and March 30, 2024, all patients aged 65 and older who applied to this pharmacy were screened, and those with at least one psychotropic medication in their prescription and who had been using any medication in the last month were included in this study. Patients with five or more medications were considered subject to polypharmacy.

Patients aged 65 years and over with a prescription for at least one psychotropic medication and who had been taking any medication for the last month were included in this study. Patients who did not have psychotropic medication on their medication and were under the age of 65 years. Patients who applied to the pharmacy with a prescription and had used no medication for the last month were excluded from the study. If the same patient was prescribed the same medication or group of medications again within the last month, only the most recent prescription was taken into account.

Data were collected between January 30 and March 30, 2024. A pharmacist screened all patients aged 65 years a week through the prescription registration system. Patients aged 65 years and over who had a prescription for psychotropic medication and who had used any medication in the last month were included in the study.

Demographic information of the patients, such as gender and age, diagnostic information, drug doses prescribed by the doctor, and frequencies of doses in the three prescriptions included in this study, were recorded on the patient profile form. Lexicomp® identified potential interactions between the psychotropic medications prescribed to these patients and the medications they had been taking for the last month. Lexicomp® classifies pDDIs into five categories according to clinical significance: A (interaction of no clinical significance), B (intervention not required), C (further monitoring required), D (treatment intervention required),

and X (contraindicated use). Drug interactions in categories D and X were considered clinically significant.

In addition, we determined PIP utilization using the American Geriatrics Society 2023 *Beers Criteria®*. The *Beers Criteria®* is the most appropriate assessment tool for a pharmacy-based study. 'The *Beers Criteria®* has five main parts: potentially inappropriate medications for use in geriatric adults, potentially inappropriate medications for use in certain diseases or syndromes, drugs that should be used with caution in geriatric adults, potentially clinically important drug–drug interactions that should be avoided in geriatric adults, and medications that require dose adjustment according to renal function in geriatric adults.[20]

The ACB Calculator® was used to determine the potential risk of anticholinergic effects (such as falls, fracture risk, confusion, and cognitive impairment) that may be caused by medications. The ACB Calculator® states that individuals with an ACB score of three or higher are at greater risk of confusion, falls, and death.

The sample size was calculated with a calculator according to a 95% confidence interval. According to the data obtained from the provincial population directorate, the population of the neighborhood where the study was conducted was taken as 8.000, and the older adult population rate was taken as 14%. Therefore, this study required the analysis of at least 181 prescriptions. This study included prescriptions from all patients who met the inclusion criteria and applied to the pharmacy within the 2-month study.

Our study was conducted under the Declaration of Helsinki. A health sciences scientific research ethics committee (number: E-13562490-050.01.04-472830, date: 30.01.2024) approved this study.

Data analyzed with Statistical Package for the Social Sciences Statistics V 23.0 (IBM, Armonk, New York, USA). According to the Kolmogorov-Smirnov test, the data were not normally distributed. The continuous variables are presented as medians (interquartile ranges, IQRs), and ordinal and nominal values are presented as n (%). Spearman's correlation analysis was done to see how the change in ACB related to the *Beers criteria®* inappropriateness, patient comorbidity, and medication use. All the data were considered statistically significant at a $p<0.05$.

RESULTS

Among the 5.374 recorded prescriptions, we evaluated 211 prescriptions that belonged to 211 patients who met the inclusion criteria. The median age of the patients was 71 IQR (68–79) years, and 151 (71.6%) of the patients were female. The median comorbidity value per patient was 3.

Table 1. Patient medication use information

Age (years), median (IQR)	71 (68–79)
Gender	
Male, n (%)	151 (71.6)
Female, n (%)	60 (28.4)
Number of comorbidities, median (IQR)	3 (1–4)
Polypharmacy, n (%)	167 (79.1)
Number of medications used in the last month, median (IQR)	7 (5–10)
Number of psychotropic medications, median (IQR)	1 (1–2)
Number of psychotropic medications prescribed inappropriate of the Beers criteria®, median (IQR)	0 (0–2)

IQR: Interquartile range; n: Number of patients.

The most common comorbidities were hypertension (n=158), hyperlipidemia (n=75), and type 2 diabetes mellitus (n=66), respectively. Table 1 presents the medication use information of the patients.

A total of 278 psychotropic medications were included in 211 prescriptions. When the prescriptions were classified according to the International Classification of Diseases, 10th Revision codes, it was observed that these medications were prescribed with the most common diagnosis of major depressive disorder. While the SSRI group of antidepressants constituted the majority of psychotropic medications, escitalopram (n=66, 23.7%) was the most frequently prescribed medication (Fig. 1a and b). We determined that the parameters that could affect patients' treatment were unaffected by gender ($p>0.05$).

The evaluation using the 2023 *Beers Criteria®* found 221 instances of inappropriate *Beers Criteria®*, with 166 of these linked to psychotropic medicines (Table 2).

A total of 815 potential interactions were detected using Lexicomp® between the psychotropic medications prescribed to the patients and those they had taken for the last month. We identified 10 of these as X, 88 as D, 605 as C, and 112 as B. The X and D interactions, which happen often between prescribed psychotropic medications and other medications, are listed in Table 3a and b because they are important and may require changes in treatment or should be avoided.

In this study, we calculated the ACB before and after the prescription of psychotropic medication for each patient. The prescription of psychotropic medication significantly increased the ACB score compared to the medications the

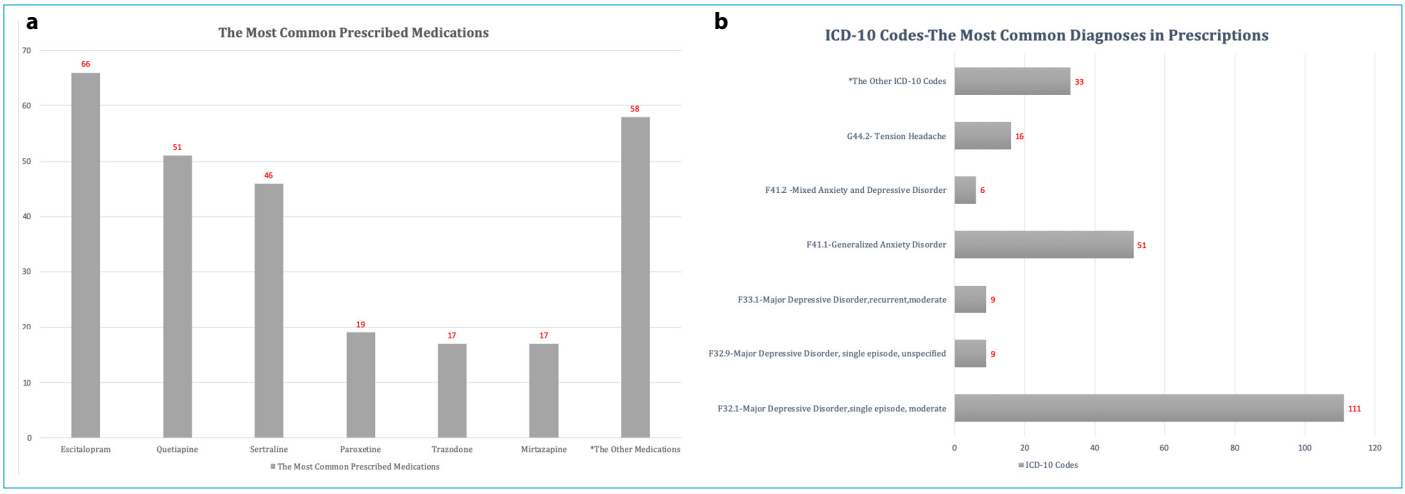


Figure 1. (a) Prescription diagnoses and medications prescribed to patients. *Duloxetine, citalopram, vortioxetine, venlafaxine, amitriptyline, olanzapine, haloperidol, hyoscine n-butyl bromide-medazepam, hydroxyzine, sodium valproate. **(b)** Prescription diagnoses of patients. *Multi-infarct dementia, schizophrenia, bipolar affective disorder, depressive disorder, recurrent depressive disorder, other specified anxiety disorders, anxiety disorder - unspecified, mixed disorders of conduct and emotions, other specified extrapyramidal and movement disorders, other Alzheimer's disease, tension-type headache, other sleep disorders.

patients took in the previous month (ACB before prescription [median (IQR)] 1 [0–2], ACB after prescription [median (IQR)] 3 [1–5], p<0.001). The relationship between the increase in ACB score and the number of inappropriate *Beers Criteria*® was looked at using the independent variables as shown in Table 4.

DISCUSSION

The main goal of this study was to find out if there are any pDDIs between psychotropic medications and other medications when given to older outpatients and to check how these medications affect the ACB score. In the study, researchers found 166 PIMs and 815 drug interactions related to psychotropic medications, and they noticed that the ACB score for older adults increased after they were prescribed psychotropic medications, changing from a median of 1 (0–2) to 3 (1–5).

Of the 452 prescriptions recorded for adults aged 65 and over, 32.5% contained at least one psychotropic medication. The results in the literature show that the rate of prescribing at least one psychotropic medication to older adults varies between 35.9% and 50.1%, similar to this study.

Anxiolytics (31–33.5%) and antidepressants (12–33.3%) are the most commonly prescribed psychotropic medications in patients with depressive syndrome. SSRIs account for 42.2% of antidepressants and are prescribed as a suitable option for older patients.[21-25] In this study, SSRIs accounted for 84.7% of antidepressants, while escitalopram was the most commonly prescribed psychotropic medication (23.7%). In this study, the number of benzodiazepine prescriptions, such as hyoscine n-butyl bromide-medazepam (3.6%), was quite low compared to all the prescriptions filled at the pharmacy.

Previous studies have only evaluated the interactions between psychotropic medications.[10] The present investigation is the first study to evaluate the interactions between psychotropic medications prescribed to older adults presenting to the pharmacy and the medications they had been taking in the last month and to identify combinations of psychotropic medications that should be avoided or modified. A total of 1705 interactions were detected between the prescribed medications and those used in the last month, 47.8% of which were between psychotropic medications and others. The majority, 74.1%, were C-level interactions requiring follow-up, while the percentages of clinically significant X- and D-level interactions were 2.5% and 9.1%, respectively. These led to the identification of drug combinations with psychotropic medications that need avoidance or modification. In this study, the most common psychotropic medication causing D-level interactions was escitalopram, while quetiapine was the most common at the X-level.

ACB scores usually increase with psychotropic medication prescriptions, but some psychotropic medications, such as duloxetine, do not affect ACB, according to the

Table 2. Top twenty PIMs among prescribed psychotropics according to the 2023 Beers criteria®

Number of inappropriate Beers criteria® 2023	PIPs	Inappropriate beers criteria® 2023
22	Quetiapine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
19	Paroxetine	Highly anticholinergic, sedating, and causing orthostatic hypotension; the safety profile of low-dose doxepin (≤6 mg/day) is comparable to that of placebo
18	Escitalopram	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
15	Sertraline	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
13	Quetiapine	Increased risk of stroke and greater rate of cognitive decline and mortality in persons with dementia. Additional evidence suggests an increased risk due to the association between antipsychotic medication and mortality, independent of dementia
10	Hyoscine N-butyl bromide-medazepam	Highly anticholinergic, uncertain effectiveness
9	Trazodone	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
8	Olanzapine	Highly anticholinergic, uncertain effectiveness
8	Paroxetine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
7	Hyoscine N-butyl bromide - medazepam	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
6	Mirtazapine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
4	Amitriptyline	Highly anticholinergic, uncertain effectiveness
4	Haloperidol	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
4	Venlafaxine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
3	Hydroxyzine	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as a hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity.
3	Olanzapine	Increased risk of stroke and greater rate of cognitive decline and mortality in persons with dementia. Additional evidence suggests an increased risk due to the association between antipsychotic medication and mortality, independent of dementia
2	Hydroxyzine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
2	Olanzapine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
2	Olanzapine	Dopamine-receptor antagonists with the potential to worsen Parkinsonian symptoms. Exceptions: Clozapine, pimavanserin, and quetiapine appear to be less likely to precipitate the worsening of Parkinson's disease than other antipsychotics
2	Vortioxetine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
1	Amitriptyline	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
1	Duloxetine	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents

Table 2. Top twenty PIMs among prescribed psychotropics according to the 2023 Beers criteria® (Cont.)

Number of inappropriate Beers criteria® 2023	PIPs	Inappropriate beers criteria® 2023
1	Haloperidol	Increased risk of stroke and greater rate of cognitive decline and mortality in persons with dementia. Additional evidence suggests an increased risk due to the association between antipsychotic medication and mortality, independent of dementia
1	Risperidone	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents
1	Sulpiride	Increased risk of falls and fractures with the concurrent use of ≥3 CNS-active agents

PIPs: Potentially inappropriate psychotropics, PIM: Potentially inappropriate medication, CNS: Central nervous system.

ACB Calculator®. Even though 10 patients did not show a change in their ACB score due to reasons like having used the same medication before or taking a medication that does not affect the ACB score, the overall analysis of all patients showed a significant increase in ACB after they were prescribed psychotropic medications (from a median of 1 (0–2) to 3 (2–5), $p<0.001$). In the results of this study, 110 patients (52.1%) had an ACB score of three or higher after psychotropic prescription, while a study published in the literature found that 64% of older patients prescribed anticholinergic medications had an ACB score of three or higher. This rate is quite low according to this study because ACB caused by psychotropic medications prescribed for older adults has not been evaluated.[26] The increase in ACB is positively correlated with age, the number of comorbidities, the number of psychotropic medications, and the number of medications used in the last month, and the correlation increases with the number of psychotropic medications, the number of comorbidities, and the number of medications used in the last month.

We evaluated patients in this study using the *Beers criteria®* for both their psychotropics and all medications. A total of 221 inappropriate medications with the *Beers criteria®* were identified, 166 (75.1%) of which were caused by psychotropic medications. The results indicate that psychotropics, when prescribed to older patients, constitute a significant portion of potentially inappropriate medication use. In parallel with the literature, this study determined the prevalence of PIPs to be 38.4% according to the 2023 *Beers Criteria®*.[22,27] The most commonly prescribed PIP is quetiapine, which is prescribed with three or more medications that act on the central nervous system and increase the risk of stroke and mortality in patients with dementia, followed by paroxetine, which causes a high ACB in older patients. The literature ranks antipsychotics, prescribed for patients with dementia, as the second group of medications not eligible for the *Beers criteria®*. Despite the special warnings for older adults, studies in the literature show that they are still prescribed to patients in this age category for dementia, sleep disorders, and non-psychotic depression conditions.[10,22,27]

Against that background, it is important to evaluate the use of psychotropic medications in older patients.

This study has several limitations, which should be recognized. First, this descriptive study had a small sample size for its assessment of the use of psychotropic medication and its identification of potential drug interactions. The small sample size in this study is primarily due to practical constraints, such as limited access to participants and available resources. Despite this limitation, appropriate methodological rigor was maintained to ensure the validity of the findings. While generalizability may be limited, the results offer helpful conclusions about the studied context. We encourage readers to interpret the findings, considering the study's scope and exploratory nature.

Second, we evaluated the possible interactions of psychotropic medications prescribed to older adults with other medications and determined if they were appropriate according to the *Beers Criteria®*. We could also not assess whether patients were taking the appropriate medication or dosage based on their kidney function, as we could not access patients' laboratory data. Therefore, we may have underestimated the number of criteria deemed inappropriate according to the *Beers criteria®*. Third, another limitation of this study is that payment conditions possibly excluded some psychotropic medications from patients' prescriptions for certain conditions.

Table 3a. The most common pDDIs of prescribed psychotropic medications

Psychotropic-Psychotropic medication combination	Psychotropic-Psychotropic pDDI frequency n, (%)	Severity class (Lexicomp®)	Mechanism of pDDI
Escitalopram-Quetiapine	15 (15.3)	D level	SSRIs may increase the adverse/toxic effects of antipsychotics QT prolongation may be observed when antipsychotics and antidepressants with QT prolongation potential are used simultaneously
Citalopram-Quetiapine	8 (8.2)	X level	QT-prolonging agents may enhance the QTc-prolonging effect of citalopram
Haloperidol-Quetiapine	5 (5.7)	D level	QT-prolonging agents may enhance the QTc-prolonging effect of haloperidol
Olanzapine-Sulpiride	1 (1.2)	X level	Antipsychotic agents may enhance the adverse/toxic effects of sulpiride
Haloperidol-Sulpiride	1 (1.2)	X level	Antipsychotic agents may enhance the adverse/toxic effects of sulpiride

Table 3b. The most common pDDIs of prescribed psychotropic medications

Psychotropic-Other medication combination	Psychotropic-Other pDDI frequency n, (%)	Severity class (Lexicomp®)	Mechanism of pDDI
Sertraline-Diclofenac	7 (7.14)	D level	SSRIs may increase the antiplatelet effect of NSAIDs, while NSAIDs may decrease the therapeutic effect of SSRIs
Escitalopram-Dexketoprofen	5 (5.1)	D level	SSRIs may increase the antiplatelet effect of NSAIDs, while NSAIDs may decrease the therapeutic effect of SSRIs
Sertraline-Enoxaparine	5 (5.01)	D level	Antiplatelets may increase the anticoagulant effect of enoxaparin, and bleeding may occur.
Quetiapine-Pramipexole	5 (5.1)	D level	Antipsychotics reduce the effectiveness of anti-Parkinson medications
Ipratropium/Salbutamol-Quetiapine	4 (4.8)	X level	Anticholinergic medications may increase the anticholinergic effect of antipsychotics
Paroxetine-Diclofenac	3 (3.6)	D level	SSRIs may increase the antiplatelet effect of NSAIDs, while NSAIDs may decrease the therapeutic effect of SSRIs
Sertraline-Ibuprofen	3 (3.6)	D level	SSRIs may increase the antiplatelet effect of NSAIDs, while NSAIDs may decrease the therapeutic effect of SSRIs
Citalopram-Naproxen	2 (2.4)	X level	SSRIs may increase the antiplatelet effect of NSAIDs, while NSAIDs may decrease the therapeutic effect of SSRIs
Tramadol-Gabapentin	2 (2.4)	D level	CNS depressant medications may increase the effect of opioid agonists on the CNS

pDDIs: Potential drug–drug interactions; CNS: Central nervous system; SSRIs: Selective serotonin reuptake inhibitors; NSAIDs: Nonsteroidal anti-inflammatory drugs; X levels: Avoid combinations; D levels: Modify regimen.

CONCLUSION

Psychotropic medication prescriptions for older adults are associated with increased drug interactions and ACB. Careful assessment using geriatric criteria is recommended to ensure safer prescribing practices. We hope that this study will enable the improvement of the treatment process for older adults by taking into account PIMs, pDDIs, and ACB. The findings of this study highlight the need for all healthcare professionals to be aware of the need for caution when prescribing psychotropic drugs to older patients.

Table 4. Correlation of the difference in anticholinergic burden and the inappropriate use of medication with patient comorbidities and medication use

	Inappropriate Beers Criteria® for psychotropic medications (Correlation coefficient)	Anticholinergic burden difference before and after prescription (Correlation coefficient)
Age	0.116	0.150*
	p=0.091	p=0.031
Number of co-morbidities	0.014	0.014
	p=0.844	p=0.837
Number of psychotropic medications	0.716**	0.632**
	p=0.000	p=0.000
Number of medications used in the last month	0.150*	0.173*
	p=0.030	p=0.013

*Spearman's correlation is significant at the 0.05 level (two-tailed); **Spearman's correlation is significant at the 0.001 level (two-tailed).

Disclosures

Ethics Committee Approval: Ethical approval for the study was obtained from the Karadeniz Technical University Health Sciences Scientific Research Ethics Committee (Approval date: January 30, 2024; File number: 2023/136).

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Conflict of Interest: None declared.

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