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Frequency of Single or Combined Anticholinergic Medication Usage as Potentially Inappropriate Medications among the Oldest-Old Age Subgroup

Fuat Nihat Özaydın

Department of Pharmacology, Istanbul Atlas University, School of Medicine, Istanbul, Turkey

ABSTRACT

Background: The use of medications with anticholinergic effects can have negative effects on older patients, such as cognitive dysfunction and falls. The aim of this study was to determine the frequency of use of anticholinergic medication among the oldest-old age group and to analyze the factors associated with its use.

Methods: This is a descriptive study. The data were collected by visiting the oldest-olds at their homes, where the oldest-olds lived alone or with his or her family. The sample size was calculated as 354 using EpiInfo. The generic name of the medication used, the age, sex, and city of residence of the patient were recorded. The medications were analyzed using guidelines showing the anticholinergic effect, classified as 1 (low), 2 (moderate), and ≥3 (strong), and the frequency of usage by the oldest-olds was determined.

Results: A total of 549 oldest-olds participated in the research. Of the oldest-olds, 57.92% (n=318) were using one or more anticholinergic medications. The median number of anticholinergic medications used by the oldest-olds was 1 (range: 0.00–6.00). Medications with strong anticholinergic effects (≥3) were used by 14.94% (n=82) of the oldest-olds. The most commonly used were medications with low anticholinergic effects. However, the concomitant use of anticholinergic medications increased the total anticholinergic effect.

Conclusion: The oldest-old age group used medications with anticholinergic effects. A strong anticholinergic effect was obtained when medications with low or moderate anticholinergic effects were combined. Medications with anticholinergic effects should also be reviewed in the safety analysis of medications used by the oldest-old.

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INTRODUCTION

Society in Turkey is aging. With aging, the incidence of single or combined noncommunicable diseases increases. The most common chronic diseases in old age are hypertension, hyperlipidemia, ischemic heart diseases, osteoarthritis, diabetes, heart failure, chronic kidney failure, and Alzheimer's disease.[1,2] Alzheimer's and other dementia diseases are in second place in the rate of increase.[2]

An important feature of the first-choice and/or frequently used medications in the treatment of these diseases is that they have low, moderate, or strong anticholinergic effects. Metformin (antidiabetic), celecoxib (NSAID), lansoprazole (proton pump inhibitor), famotidine, ranitidine (H2 receptor antagonist), fluticasone/salmeterol, ipratropium, tiotropium (respiratory system antimuscarinic drugs), benzodiazepines, antipsychotics, selective serotonin reuptake inhibitor (SSRI) class antidepressants, selective beta1 blockers such as metoprolol, atenolol, furosemide (diuretic), diltiazem (nondihydropyridine calcium channel blocker), and warfarin (oral anticoagulant) are the first choice or frequently used medications with anticholinergic effect in the treatment of these diseases.[3,4]

Anticholinergic medications inhibit the binding function of acetylcholine, a neurotransmitter, to muscarinic receptors. The blood-brain barrier is weakened in older people. Therefore, in addition to peripheral effects, such as dry mouth, dry eyes, constipation, and urinary retention, they cause central nervous system-based side effects such as dizziness, falling, and cognitive impairment.[4,5] Anticholinergic medications are included in the potentially inappropriate medication class because the risk of side effects may be higher than their therapeutic benefits.[5-7]

Corresponding author: Fuat Nihat Özaydın, e-mail: fnozaydin@gmail.com

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As a result, the medication-induced anticholinergic effect was found to be associated with falling, poor cognitive function, functional decline, and increased mortality, especially in the older.[8]

The oldest-old are defined as 85 years of age and over.[9] This is the age period in which more than 1 treatment and many medications are used due to the increased number of chronic diseases.[10] In the oldest-old, hospitalization is more frequent, the hospital stay is longer, and mortality is higher.[9] Since the physiological reserve decreases in the oldest-old, the risk of adverse medication effects is highest, even if used at recommended doses.[11]

Caring for Alzheimer's disease and other noncommunicable diseases in the oldest-old group is difficult and costly. It is important to take preventive measures and to prevent or delay complications if there is a disease. One of the preventive measures is not to use medications with anticholinergic effects in the oldest-old, to use medications with low anticholinergic effects if necessary, and to prefer combinations with low anticholinergic effects in the case of multiple medication use.[4-8] The aim of this study was to determine the frequency of anticholinergic medication usage in the oldest-olds, anticholinergic effect classification, and also to analyze the factors associated with its use.

MATERIAL AND METHODS

This research was a descriptive study. Data were collected between December 2021 and May 2022. Students enrolled in a medical undergraduate program at a university and taking a pharmacology course were selected as interviewers. After a course on the basic principles of pharmacology (introduction to pharmacology, pharmaceutical forms of medications, routes of administration), 120 students agreed to participate in the study as interviewers. In 2021, the older population in Turkey was 8,245,124, and 8% (n=659 609) of the older were in the oldest-old group (born in 1936 and before).[12] Using the Open EpiInfo program, the sample size was calculated as 384 for this study.[13] The snowball sampling method was used due to the low number of oldest-olds in Turkey and their distribution throughout the country.[14] The research was conducted throughout Turkey. The interviewers visited the oldest-olds in their homes. Oldest-olds staying in inpatient institutions, such as hospitals and nursing homes, were not included in the study. The generic name of the medications, the patient's age, sex, and city of residence were recorded. Oral, parenteral, and inhaled medications were included in the study. An explanation of the research was given to the oldest-olds and to family members if they were caring for the oldest-olds, and informed consent was obtained from all participants included in the study. The final sample was a nonprobability sample.

Different published guidelines have been used to identify medications with anticholinergic effects. To detect anticholinergic medications in the potentially inappropriate medication group, the Beers 2019, which was prepared according to explicit criteria and required minimum information about the clinical findings of older patients, was used.[7] Twenty-two different lists classify medications according to their anticholinergic effects.[15] A review [published in 2020 describing the Anticholinergic Activity Scale (AAS), Anticholinergic Burden Classification (ABC), Anticholinergic Cognitive Burden (ACB), Anticholinergic Drug Scale (ADS), Anticholinergic Loading Scale (ALS), and Anticholinergic Risk Scale (ARS) lists] and the CRIDECO Anticholinergic Load Scale list (CALS) [published in 2022 describing Duran Scale (DS), Salahudeen Scale (SS), German Anticholinergic Burden Scale (GABS), and Korean Anticholinergic Burden Scale (KABS)] were used for the anticholinergic analysis of medications.[3,4] If the anticholinergic effect of the medication was shown differently in these lists, the value shown in the CALS was taken as the final reference.[4]

The anticholinergic effects of the medications were classified into 3 groups: group 1=a low anticholinergic effect, group 2=a moderate anticholinergic effect, and group ≥3=a strong anticholinergic effect.[3,4,15] If a medication was not included in these groups, it was considered unknown or had no anticholinergic effect. In the case of concomitant use of anticholinergic medications, the anticholinergic effect of each medication was summed arithmetically and expressed as the total anticholinergic effect.[15]

A 5-year age classification was made for the oldest-olds. The provinces where the oldest-olds lived in Turkey were classified into 5 regions: Western region: Aydın, Balıkesir, Bursa, Canakkale, Denizli, İstanbul, Izmir, Kırklareli, Kocaeli, Manisa, Muğla, Sakarya, Tekirdağ, Yalova (Marmara and Aegean regions); Southern region: Antalya, Adana, Burdur, Hatay, Isparta, İçel, K.Maraş, Osmaniye (Mediterranean region); Central region: Afyon, Amasya, Ankara, Bilecik, Bolu, Çankırı, Çorum, Eskişehir, Kayseri, Kırşehir, Konya, Kütahya, Nevşehir, Niğde, Sivas, Tokat, Uşak, Yozgat, Aksaray, Karaman, Kırıkkale, Düzce (Central Anatolia region); Northern region: Artvin, Giresun, Gümüşhane, Kastamonu, Ordu, Rize, Samsun, Sinop, Trabzon, Zonguldak, Bartin, Karabük (Black Sea region); Eastern Region: Adıyaman, Ağrı, Bingöl, Bitlis, Diyarbakır, Elazığ, Erzincan, Erzurum, Gaziantep, Hakkari, Kars, Malatya, Mardin, Muş, Siirt, Tunceli, Şanlıurfa, Van,

MAIN POINTS

- Among the oldest-olds, medications with anticholinergic effects were commonly used.
- When medications with low anticholinergic effects were used together, they induced strong anticholinergic effects.
- The frequency of anticholinergic medication use was higher in the oldest-olds using multiple drugs.

Bayburt, Batman, Şırnak, Ardahan, Iğdır, Kilis (Eastern and Southeastern Anatolia region).[16]

Ethical approval was obtained from the Ethics Committee of Istanbul Okan University (Approval No: 141, Date: September 8, 2021) analyze the frequency of potentially inappropriate medications used by the oldest-olds according to the Beers Criteria, and the data was collected. Later, a new ethical approval from the same committee was obtained for using these data to analyze medications with low, moderate, and strong anticholinergic effects (24.08.2022/157). The data collected from the oldest-olds included so many variables, and some parts of these data will be analyzed in some more articles for potentially inappropriate medication usage and drug-drug interactions.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences Statistics software, version 19.0 (IBM SPSS Corp.; Armonk, NY, USA). In descriptive analyzes, data on categorical variables were expressed in the form of n (%). The Kolmogorov-Smirnov test was performed as a normality test. Nonparametric tests were used because the continuous data were not normally distributed. Nonparametrically distributed ones were presented as median, minimum, and maximum values. Mann-Whitney *U*, Kruskal-Wallis, and Pearson chi-square tests and Fisher-Freeman-Halton exact test were performed, and Spearman's correlation coefficient was calculated. If $P < .05$, the results were considered statistically significant.

The concordance among the 2 criteria was calculated using the kappa test (values of kappa >0.75 indicate good to excellent agreement; values between 0.40 and 0.75 indicate moderate agreement; values <0.40 indicate poor agreement).[17]

RESULTS

Data were collected from 549 people who were classified as the oldest-old. The median age of the participants in the study was 88.00 (minimum = 85, maximum = 102; n = 549). Of the participants, 61.20% (n = 336) were women. The median age of the women was 88.00 (minimum = 85, maximum = 101), and the median age of the men was 88.00 (minimum = 85, maximum = 102). The distribution of males and females in age groups was similar ($P = .341$, Table 1). The distribution of men and women across regions was also similar ($P = .826$, Table 1). Due to the decrease in the number of people of advanced age in society, only 6 oldest-olds aged 100 and over were included in the study. The sociodemographic characteristics of the participants are shown in Table 1.

The median number of anticholinergic medications used by the oldest-olds was 1.00 (minimum = 0.00, max = 6.00). These were found to be similar for both sex groups ($P = .907$, Table 2). The median number of anticholinergic medications used in the 85-89 age group was 1.00 (minimum = 0.00; max = 6.00) and 0.00 (minimum = 0.00, maximum = 1.00) in the 100 and older age group ($P = .416$, Table 2). The number of anticholinergic medications used by the oldest-olds living in different regions in Turkey was found to be similar ($P = .552$, Table 2).

More than half of the oldest-olds (57.92%, n = 318) were using 1 or more anticholinergic medications. Anticholinergic medication use was similar in both sexes ($P = .775$, Table 3). Though the use of anticholinergic drugs was found to be less in the oldest-olds at the age of 100 and over, there

Table 1. Sociodemographic Characteristics of the Participants

	Sex			*P*
	Male	Female	Total	
	n (%)	n (%)	n (%)	
Age groups (years of age)				
85-89	151 (41.14)	216 (58.86)	367 (100.00)	.341
90-94	45 (33.09)	91 (66.91)	136 (100.00)	
95-99	14 (35.00)	26 (65.00)	40 (100.00)	
100-104	3 (50.00)	3 (50.00)	6 (100.00)	
Regions				
West	177 (39.07)	276 (60.93)	453 (100.00)	.826
South	5 (33.33)	10 (66.67)	15 (100.00)	
Central	5 (55.56)	4 (44.44)	9 (100.00)	
North	14 (36.84)	24 (63.16)	38 (100.00)	
East	12 (35.29)	22 (64.71)	34 (100.00)	
Total	213 (38.80)	336 (61.20)	549 (100.00)	

Table 2. Distribution of the Average Number of Anticholinergic Medications Used by Participants According to Sociodemographic Variables

	Anticholinergic Medications		
	n	Median (Minimum-Maximum)	*P*
Average number per person	549	1.00 (0-6)	
Sex			
Female	336	1.00 (0-6)	.907
Male	213	1.00 (0-5)	
Age groups (years of age)			
85-89	367	1.00 (0-6)	.416
90-94	136	1.00 (0-4)	
95-99	40	1.00 (0-4)	
100-104	6	0.00 (0-1)	
Regions			
West	453	1.00 (0-5)	.552
South	15	1.00 (0-2)	
Central	9	0.00 (0-3)	
North	38	1.00 (0-6)	
East	34	1.00 (0-3)	

Table 3. Distribution of Participants Using and not Using Anticholinergic Medications by Sociodemographic Variables

	Anticholinergic Medication			
	Not using	Using	Total	*P*
	n (%)	n (%)	n (%)	
Sex				
Male	88 (41.32)	125 (58.68)	213 (100.00)	.775
Female	143 (42.56)	193 (57.44)	336 (100.00)	
Age groups (years of age)				
85-89	153 (41.69)	214 (58.31)	367 (100.00)	.541
90-94	55 (40.44)	81 (59.56)	136 (100.00)	
95-99	19 (47.50)	21(52.50)	40 (100.00)	
100-104	4 (66.67)	2 (33.33)	6 (100.00)	
Regions				
West	188 (41.50)	265 (58.50)	453 (100.00)	.893
South	6 (40.00)	9 (60.00)	15 (100.00)	
Central	5 (55.56)	4 (44.44)	9 (100.00)	
North	16 (42.11)	22 (57.89)	38 (100.00)	
East	16 (47.06)	18 (52.94)	34 (100.00)	
Total	231 (42.08)	318 (57.92)	549 (100.00)	

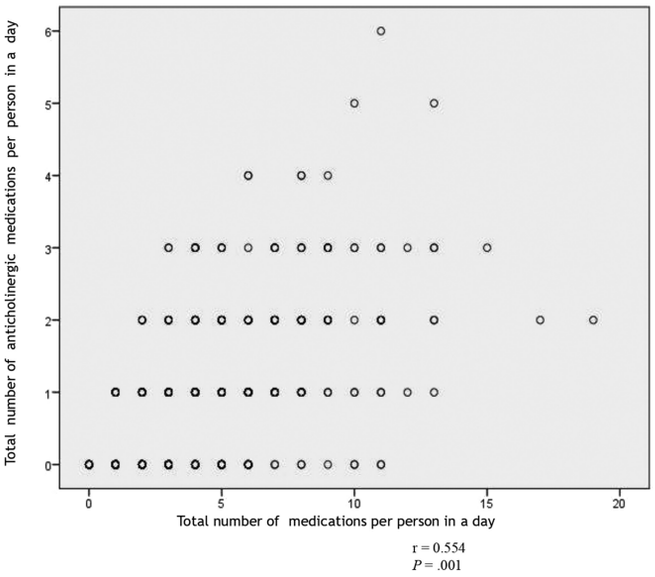

Figure 1. Relationship between the total number of medications used and the total number of anticholinergic medications used.

was no correlation between the age and the total number of anticholinergic medication usage (r=−0.057, *P*=.182, Spearman's correlation coefficient). The ages of the oldest-olds using and not using anticholinergic medications were found to be similar (*P*=.541, Table 3) Similar to age distribution, the anticholinergic medication usage was found to be similar among the oldest olds living in different regions of Turkey (*P*=.893, Table 3).

There was a positive, statistically significant correlation between 'the number of medications used' and 'number of anticholinergic medication used (r=0.554; *P* = .001, Figure 1). Among all participants, 4.92% (n=27) of the oldest-olds were using medications in group 3, 13.30% (n=73) were using medications in group 2, and 49.91% (n=274) were using group 1 anticholinergic medications. The total anticholinergic effect was higher when more than 1 anticholinergic medication was used together. The total anticholinergic effect was ≥3 in 14.94% (n=82) of the oldest-olds, 2 in 14.21% (n=78), and 1 in 28.78% (n=158) using anticholinergic medications together. In oldest-olds who used anticholinergic drugs together, ≥3 anticholinergic effects were detected more.

The most commonly used medications with anticholinergic effects were metoprolol, metformin, quetiapine, escitalopram, and furosemide molecules, respectively (Table 4). While group 1 anticholinergic medications were frequently used in the 85-99 age group, group 3 anticholinergic medications were used mainly in the younger age group (85-89 years).

According to the Beers guideline, 6.56% (n=36) of the oldest-olds were using strong anticholinergic drugs. When the medications were examined according to the anticholinergic guidelines, only 5 of the oldest-olds were using strong (group ≥3) anticholinergic medications (propiverine, tizanidine, darifenacin, and amitriptyline) in addition to the medications specified in the Beers 2019 (7.47%, n=41). However, according to the anticholinergic guidelines, the rate of usage by the oldest-olds with a total anticholinergic effect ≥3 due to

Table 4. Top Five Most Commonly Used Medications According to Anticholinergic Effect Classification

Group 1		Group 2		Group 3	
Name of Anticholinergic Medication	n (%)	Name of Anticholinergic Medication	n (%)	Name of Anticholinergic Medication	n (%)
Metoprolol	75 (19.48)	Quetiapine	40 (48.19)	Chlorpheniramine	6 (23.08)
Metformin	63 (16.36)	Olanzapine	13 (15.56)	Fesoterodine	3 (11.54)
Escitalopram	33 (8.57)	Pseudoephedrine	9 (10.84)	Hydroxyzine	3 (11.54)
Furosemide	25 (6.49)	Haloperidol	8 (9.65)	Cyproheptadine	3 (11.54)
Lansoprazole	24 (6.23)	Tramadol	4 (4.82)	Propiverine	2 (7.69)
Others	165 (42.87)	Others	9 (10.84)	Others	9 (34.61)
Total	385 (100.00)	Total	83 (100.00)	Total	26 (100.00)

the single or combined use of medications belonging to groups 1, 2, and 3 was higher (14.94%, n = 82). The kappa statistic for the Beers Criteria and the anticholinergic guidelines indicated moderate coherence ($\kappa = 0.571$, $P < .001$). According to Beers 2019 and anticholinergic guidelines, only 2 oldest-olds (0.36%) had a strong anticholinergic + anticholinergic medication combination (paroxetine + olanzapine, paroxetine + solifenacin).

In our study, 7.66% (n = 42) of the oldest-olds were using 1 or more medications with anticholinergic effects together with acetylcholine esterase inhibitors (donepezil, rivastigmine) and/or memantine, which were indicated for the treatment of Alzheimer's and other dementia diseases. The total anticholinergic effect was ≥3 in 52.83% (n = 28) of this group.

DISCUSSION

This is the first national study investigating the use of anticholinergic medications in the oldest-old group and examining the relationship between sex, geographic region, and age groups. The number of studies conducted with the oldest-olds on an international scale is small. In a study published in 2012, the health records of the 86 721 oldest-olds (mean age 85.6, SD = 7.2) staying in nursing homes were examined.[18] It was determined that 12.14% (n = 10 532) of the oldest-olds were using medications with an anticholinergic effect ≥3, while in our study, the rate was found to be 14.94% (n = 82). In another study in which 200 oldest-olds (88.3 ± 5.7) were examined, the rate of anticholinergic medication usage during hospitalization and discharge was found to be 39.50% (n = 79) vs. 44.50% (n = 89), respectively.[19] In our study, the rate of the oldest-olds using anticholinergic medications was 57.92% (n = 318), and the use of anticholinergic medications according to the ARS was also examined. The frequency of low anticholinergic medication usage was 60.50% vs. 55.50%, the frequency of moderate anticholinergic medication usage was 35.00% vs. 42.50%, and the frequency of strong anticholinergic medication was 4.50% vs. 2.00%. In our study, 49.91% (n = 274) of the oldest-olds used low anticholinergic medications, 13.30% (n = 73) used moderate anticholinergic medications, and 4.92% (n = 27) used strong anticholinergic medications.

In a study published in 2020, the anticholinergic medication used by the older (65+) between 1990-1993 (n = 7635) and 2008-2011 (n = 7762) was investigated using the ACB and classified according to age groups.[20] While the frequency of use of anticholinergic medications was 53.80% in the 85-89 age group and 50.70% in the 90+ age group in the first date interval, it showed an increasing trend in the second date interval, at 72.10% and 75.50%, respectively. In our study, the use of anticholinergic medications was 58.31% (n = 214) in the 85-89 age group and 57.14% (n = 104) in the 90+ age group. In this study, the frequency of anticholinergic medication usage according to cognitive function was also investigated. The use of medications with strong anticholinergic effects was found to be higher in the oldest-olds with impaired cognitive function.

In a study published in 2019, the medications used by 4134 elderly people with Alzheimer's disease (mean age: 81.50 ± 8.16 years) were analyzed.[21] Age >85 years was associated with a high risk of having an anticholinergic burden ≥3 points (OR 2.19; 95% CI, 1.159-4.162) and potential interactions between cholinesterase inhibitors and anticholinergic drugs were identified in 7.8% of patients in this study. The high use of strong anticholinergic medications in the oldest-olds with cognitive impairment was found to be a common feature in studies, including our study.[20,21]

In the studies examined, including ours, medications with an anticholinergic effect of 1 were frequently used by the oldest-olds. In particular, cardiology medications such as metoprolol, atenolol, and warfarin; acid secretion suppressant medications such as lansoprazole, famotidine, and ranitidine; diabetes medications such as metformin; painkillers such as celecoxib; and SSRI antidepressant medications such as escitalopram had an anticholinergic effect of 1 and were being used frequently.[3,4,15] In large-scale studies, no findings showing the negative anticholinergic effects of medications with an anticholinergic strength of 1 have been found.[21,22] However, preliminary findings have been published showing that the risk of dementia increases with the use of antidepressants with an anticholinergic effect of 1.[22] Close follow-up of the oldest-old is vital in the long-term use of medication with an anticholinergic effect of 1, as the blood–brain barrier weakens and they are more sensitive to drug adverse effects. When anticholinergic medications are used together, they can create strong anticholinergic effects. The concomitant use of 3 medications with an anticholinergic effect of 1 (e.g., metformin + metoprolol + warfarin) causes strong total anticholinergic effects in the oldest-old.[15] Studies have also been published showing that medication with a moderate anticholinergic effect negatively affects cognitive function. The adverse effects of medications with strong anticholinergic effects (≥3) are known.[23,24]

Beers 2003, 2012, and 2015 were compared with anticholinergic medication guidelines. Even though the compatibility between the new dated guideline of Beers and the anticholinergic medication guidelines increased, there was a difference, and the agreement was found to be weak–moderate.[25] This study was the first national/international study to compare Beers 2019 with the anticholinergic medication guidelines for the oldest-olds. In our study, the determination of strong anticholinergic medications and their combinations was compatible with the anticholinergic medication guidelines and Beers 2019. However, the formation of a strong total anticholinergic effect with the use of medications with low or moderate

anticholinergic effects was shown only in the analysis of anticholinergic medication guidelines.[15] Demonstrating the necessity of guidelines measuring the anticholinergic effect in the safety evaluation of medications used by the oldest-olds was the original aspect of this study.

The strength of this study was that the ACB, ADS, and ARS guidelines were widely used for the anticholinergic analysis of medications used by older adults and could be applied in observational studies. These guidelines have been validated for adverse effects. The ACB and GABS scales received the highest quality evaluation scores.[3,4] Anticholinergic evaluations of almost all medications used by the oldest-olds was carried out with a large number of guidelines in this study.

The weakness of this study was that the selected sample did not represent the oldest-olds in Turkey. Diseases existing in the oldest-olds using medication could not be identified. A dose analysis of the medication claimed to be used was not performed. It is possible that some of the participants had medical conditions that required the use of anticholinergic medications, which would make it difficult to determine whether the use of these medications was inappropriate. The relationship between the anticholinergic medications used and the clinical findings of possible adverse effects has not been investigated. No follow-up studies have been conducted to detect possible adverse effects in the oldest-olds. The answers were the statements of the participants. It was possible to give incorrect or incomplete answers to the questions due to forgetfulness.

Low/moderate-acting anticholinergic medications, alone or in combination, were frequently used in the oldest-olds, and they produced a strong total anticholinergic effect when used together. The use of guidelines showing anticholinergic medications while prescribing or controlling in the oldest-old is necessary for the success of the treatment and the prevention of undesirable effects.[15,26] There is a need for new studies investigating the frequency of use of anticholinergic medications and their anticholinergic effects among the oldest-olds in Turkey.

Ethics Committee Approval: This study was approved by Ethics Committee of Istanbul Okan University (Approval No: 141, Date: September 8, 2021).

Informed Consent: The oldest-old participants provided their written informed consent to participate in this study.

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