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Original article

Elderly care: Commonly prescribed gastrointestinal drugs associate with cognitive decline

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Abstract: *Background* — Gastrointestinal (GI) medications are among the most common drugs used in old age. Recent studies reported heterogeneous association between proton pump inhibitors (PPIs) with neurological complications such as memory impairment.
Objective — This research was conducted to assess the effect of different categories of GI drugs on cognitive function of older adults.
Methods — This case-control study was carried-out on adults 60 or more years of age and over living in Amirkola, northern Iran, where health-related data were available in the database of the second phase of the Amirkola Health and Ageing Cohort Project (AHAP). Cognitive function of the elderly was examined with the Mini-Mental State Examination (MMSE) screening test.
Results — Among 900 examined individuals, total intake of GI medications exhibited no significant effect on cognitive function of older adults [adjusted OR:1.049 (95% CI: 0.757-1.452); p=0.775]; however, a statistically significant effects of PPIs [adjusted OR=1.571 (1.001-2.467); p=0.050) and medicinal drugs affecting GI tract movements [adjusted OR=2.202 (1.180-4.111); p=0.013) on cognitive function were observed.
Conclusion — Although total intake of GI medications did not cause a statistically significant impact on cognitive function of older adults, PPIs and medicinal drugs affecting GI tract movements had a significant effect.

Keywords: elderly, cognition, pharmaceutical preparations, digestive system.

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Introduction

As people get older, the brain becomes more sensitive to central nervous system (CNS)-active medications, and the risk of cognitive side-effects following the use of these drugs increases [1, 2].

Gastrointestinal (GI) changes are common in older adults, some of them are physiological, and some are pathological [3, 4]. Different functions of the GI system, including motility, secretion of hormones and enzymes, digestion, and absorption could be affected with ageing. Furthermore, the absorption and metabolism process of different drugs could be changed in the elderly population [3]. High prevalence of various GI conditions (constipation [5], inflammatory bowel diseases [6], gastroesophageal reflux disease [5], and peptic ulcer diseases [7]) has been reported among senior adults. The age-standardized prevalence rate of peptic ulcer disease increases with age, peaking at 80–84 years in both genders [7]. These conditions increase, both due to ageing-related processes, and due to the increased effects of comorbidities as well as exposure to environmental factors such as drugs, alcohol consumption and tobacco use [4]. Although the number of older people suffering from GI symptoms is significant, limited information is available on different health-related aspects of these complaints [8].

Gastrointestinal manifestations and medications are among the most important issues in old age, as GI symptoms can be caused by various drug regimens or can be alleviated by taking appropriate medications. Also, GI drugs such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists are among the most commonly used drugs in the American elderly [9]. Adverse effects of GI drugs range from mild clinical complaints such as diarrhea to severe and fatal GI bleeding and perforation, and can reduce the quality of life of the elderly, leading to disability, mortality and medical costs [10]. Recent studies showed an association between PPI drugs with a wide range of neurological complications such as hearing loss, visual impairment, migraine headaches and memory impairment [11].

Cognitive disorders are considered among the most prevalent psychiatric disorders in old age. Some medications such as vitamin D exhibit positive effects on the cognitive functions in this population, and some other medicines (such as antidepressants and benzodiazepines) have negative impacts on the cognition. However, in general, limited evidence is available on the impact of different drugs on the cognitive function of older adults, and different studies reported different findings [12-14]. Some studies have suggested that PPIs may play a role in the development of cognitive impairment due to their effect on the CNS, and the

increased production of extracellular amyloid plaques and tau protein [15].

Given a very limited number of studies on the pharmacoepidemiology of GI drugs and its correlation with cognitive disorders in the elderly, this research was designed to evaluate this issue.

Material and Methods

Study design and settings

This case-control study was carried-out on senior adults aged 60 year and over living in Amirkola, northern Iran, whose health-related data were available in the database of the second phase of Amirkola Health and Ageing Cohort Project (AHAP) [16]. All elderly people living in this region were invited to participate in the research. Public announcement for participation was performed through local health-centers, family physicians, mosques, and other public places attended by older people.

Participants

The inclusion criteria were: age 60 and over; living in the city of Amirkola; and availability of medical information regarding the elderly in the database of the second phase of AHAP cohort study.

All participants were assessed in terms of their cognitive function and were divided into the study group and control group (with and without cognitive impairment, respectively). Given the impact of age and gender on cognitive function of older adults [17], these two groups were adjusted for age and gender. Subsequently, taking different GI drugs was assessed based on the profile of cognitive performance. Flow chart of the research design is presented in *Figure* 1.

Outcomes and assessment of variables

At baseline examination, general characteristics, including age, sex, marital status, level of education, and history of tobacco use, were collected through direct interviews with study participants. Since the people of this region are generally Muslim and do not consume alcohol, their history of alcohol drinking was not questioned. The number of chronic comorbidities and the name of taken medicinal drugs were investigated by observing and reviewing the person's medications, and investigating medical history via interviewing the participant or his/her family members who had information about previous medical disorders and prescribed medications.

Gastrointestinal drugs taken by the older adults were classified into four groups: 1 – antiemetic drugs, 2 – drugs affecting GI tract movements, laxatives or anti-diarrheal agents, 3 – medications used for acid peptic disease, including proton pump inhibitors, 4 – others (e.g., anti-inflammatory drugs for inflammatory bowel disease) [18].

Obesity and overweight were defined based on the body mass index (BMI: weight in kilograms divided by the square of their height in meters) and the classification of the World Health Organization. Accordingly, BMI from 25.0 to 29.9 kg/m2 was considered as overweight and its values ≥30 were interpreted as obesity [19].

The presence of depressive symptoms was assessed using the short form of Geriatric Depression Scale (GDS). This questionnaire has 15 items. A score of 0-4 implied a normal mood, while 5-8, 9-11, and 12-15 points represented mild, moderate, and severe depressive symptoms, respectively [20].

Cognitive function of the elderly was examined with the Mini-Mental State Examination (MMSE) test. This questionnaire evaluates five domains of cognition including orientation, repetition, attention and calculation, verbal recall, and language. If the elderly scored 25 or more, it was considered normal. Scores of 21-24, 10-20, and ≤9 were classified as mild, moderate, and severe cognitive impairment symptoms, respectively [20].

Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE). This questionnaire examines the intensity, duration and frequency of different physical activities during the last week. A higher score indicates more physical activity [21].

All questionnaires were completed by trained staff.

Sample size

Given a confidence level of 95% and a power of 80% and assuming p1=10% and p2=5% regarding the frequency of PPI use in groups with and without cognitive impairment, the number required sample sizes for each group were estimated at 432.

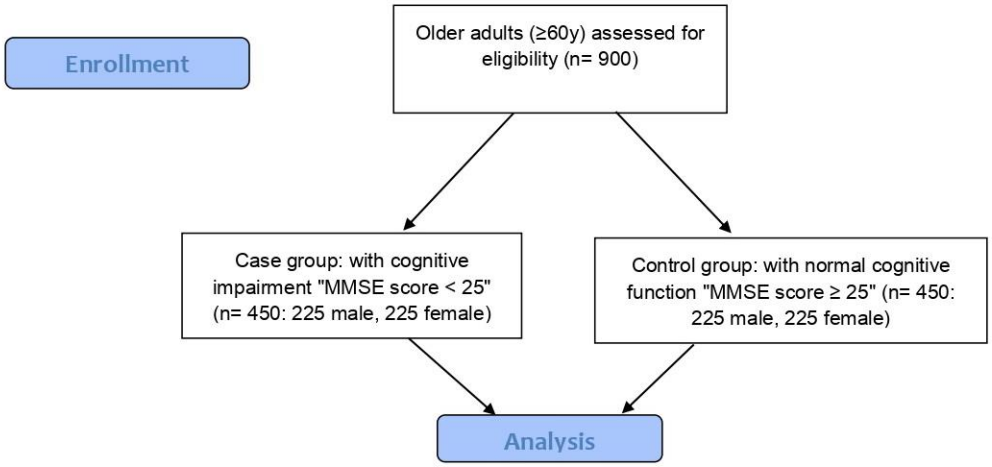

Figure 1. Flow chart of the research design.

Adjusted for age and gender, the two study groups included 450 older adults (225 male and 225 female) each with MMSE score less than 25 (the case group) and ≥25 (the control group). The age structure of people who were recruited in these two groups were similar to that of the local population: 60-64 years old (n=72 in each group), 65-69 years old (n=112), 70-74 years old (n=114), 75-79 years old (n=75), 80-84 years old (n=59), and 85-89 years old (n=18).

Statistical methods

Data analysis was performed using SPSS-17 software package. T-test, chi-square, and logistic regression were employed for data analysis. P-value ≤ 0.05 was assumed to represent statistically significant patterns.

Results

Among 900 examined senior adults, mean ages in the case group (with cognitive impairment) and the control group (with a normal cognitive function) were 72.07±7.27 years and 71.78±7.35 years, respectively (p=0.547). Baseline characteristics of the two study groups are presented in *Table* 1.

Mean numbers of medicinal drugs (including GI and non-GI medications) which the participants were taking were 3.83±3.29 in the case group, and 3.84±3.04 in the control group (p=0.958); mean numbers of diagnosed comorbid disorders were 4.19±2.40 and 3.64±2.22 (p<0.001), respectively; mean BMI values were 28.53±5.21 and 28.18±4.97 kg/m2 (p=0.307), correspondingly; and mean PASE scores were 86.22±55.55 and 98.46±57.24 (p=0.001) for the case group and the control groups, respectively.

Among the four defined groups of GI drugs, medications used for acid peptic disease have been used more than other groups: 190 study participants (21.1%) were taking these drugs. PPIs have been administered more frequently than other GI medications; 102 (11.3% of the elderly) were taking them. Distribution of administration of GI drugs in different groups of older adults (based on the cognition function) is presented in *Table* 2. This table reveals a significant association of PPI intake (p=0.018) and GI tract movement drugs intake (p=0.003) with a cognitive function of senior adults, albeit no significant association was found between the total intake of GI medications and cognition (p=0.333).

After logistic regression analysis and including potential confounding variables (marital status, number of comorbid disorders, history of tobacco use, number of taken medications, BMI, and physical activity) in the model, total intake of GI medications exhibited no significant effect on cognitive function of older adults (p=0.775); meanwhile, physical activity (p=0.034), the number of comorbid disorders (p<0.001), and the number of drugs the person was taking (p=0.006) showed significant effects.

Values of crude and adjusted odds ratio (OR) of different GI medications on cognitive decline of older adults are presented in *Table* 3. This table demonstrates the significant effect of PPIs (adjusted OR=1.571; p=0.050) and drugs affecting GI tract movements (adjusted OR=2.202; p=0.013) on cognitive function in old age.

Discussion

Our findings revealed a notable prevalence of GI drug consumption in older adults: 27.2% of the participants were taking these medicines. Among GI medications, anti-ulcer agents were used more than others; and among anti-ulcer drugs, PPIs were the most consumed ones. The research focus in most previously published studies included GI changes, GI disorders, side-effects of different medications on GI system, polypharmacy or inappropriate medications in the elderly [3-5, 8, 22-26]. A few studies reported the current situation with using different categories of GI drugs in this population. Kochar et al. reported that almost 40% of patients in GI practices in the United States were 60 years or older [5]. Varghese et al.' s study represented that although people aged 65 and over comprised about 14% of the total population in the U.S., they accounted for over one-third of the total outpatient drug prescription in this country [27]. Another AHAP-related research conducted among senior adults in northern Iran investigated that only 32.5% of the elderly consumed no medication, and 23.1% of the examined people practiced polypharmacy. Gastrointestinal medications were reported as the third most prevalent drug category (after cardiovascular, and analgesic anti-inflammatory drugs) that older female adults consumed [28].

Table 1. Baseline characteristics of the two study groups

Characteristics		*Cognitive function*		*P-value*
		Impaired (The case group) n=450 Number (%)	Normal (The control group) n=450 Number (%)	*(Chi-square test)*
Level of education	Illiterate	398 (63.0)	234 (37.0)	<0.001
	Elementary education	42 (26.1)	119 (73.9)	
	High school education	8 (10.0)	72 (90.0)	
	College education	2 (7.4)	25 (92.6)	
Marital status	Married	358 (50.3)	354 (49.7)	0.806
	Unmarried	92 (48.9)	96 (51.1)	
History of tobacco use	No	395 (50.5)	387 (49.5)	0.489
	Yes	55 (46.6)	63 (53.4)	
PASE* score	<150	387 (51.9)	358 (48.1)	0.013
	≥150	63 (40.6)	92 (59.4)	
Body mass index (kg/m2)	<25	116 (48.3)	124 (51.7)	0.379
	25-29.99	164 (48.2)	176 (51.8)	
	≥30	170 (53.1)	150 (46.9)	
Taking GI drugs	No	326 (49.8)	329 (50.2)	0.881
	Yes	124 (50.6)	121 (49.4)	

*PASE, Physical Activity Scale for the Elderly.

Table 2. Distribution of gastrointestinal drug use in older adults based on their cognition function

Type of GI drugs		*Cognitive function*				*P-value (Chi-square test)*
		Normal (The control group) n=450 Number (%)	Impaired (The case group)			
			Mild n=261 Number (%)	Moderate n=182 Number (%)	Severe n=7 Number (%)	
Medications used for acid peptic disease	No (n=710)	351 (49.4)	210 (29.6)	143 (20.1)	6 (0.8)	0.349
	Yes (n=190)	99 (52.1)	51 (26.8)	39 (20.5)	1 (0.5)	
PPIs*	No (n=798)	409 (51.3)	228 (28.6)	155 (19.4)	6 (0.8)	0.018
	Yes (n=102)	41 (40.2)	33 (32.4)	27 (26.5)	1 (1.0)	
Drugs affecting GI tract movements, laxatives, or anti-diarrheal agents	No (n=850)	443 (50.9)	245 (28.8)	167 (19.6)	5 (0.6)	0.003
	Yes (n=50)	17 (34.0)	16 (32.0)	15 (30.0)	2 (4.0)	
Antiemetic drugs	No (n=894)	447 (50.0)	258 (28.9)	182 (20.4)	7 (0.8)	0.359
	Yes (n=6)	3 (50.0)	3 (50.0)	0	0	
Total intake of GI drugs	No (n=655)	329 (50.2)	192 (29.3)	129 (19.7)	5 (0.8)	0.333
	Yes (n=245)	121 (49.4)	69 (28.2)	53 (21.6)	2 (0.8)	

*PPIs, Proton pump Inhibitors.

Table 3. Crude and adjusted* odds ratio of GI medications on cognitive decline of older adults

Type of GI drugs	*Crude odds ratio (95% CI)*	*P-value*	*Adjusted odds ratio (95% CI)*	*P-value*
Medications used for acid peptic disease	0.899 (0.652-1.238)	0.513	0.878 (0.620-1.244)	0.465
Proton pump Inhibitors	1.564 (1.028-2.379)	0.037	1.571 (1.001-2.467)	0.050
Drugs affecting GI tract movements, laxatives, or anti-diarrheal agents	2.016 (1.106-3.674)	0.020	2.202 (1.180-4.111)	0.013
Antiemetic drugs	1.000 (0.201-4.981)	0.999	1.262 (0.245-6.450)	0.780
Total intake of GI drugs	1.034 (0.771-1.387)	0.822	1.049 (0.757-1.452)	0.775

* Marital status, the number of comorbid disorders, history of tobacco use, the number of drugs the person was taking, BMI, and physical activity were considered in the model.

This research showed no significant effect of the total intake of GI drugs on cognitive decline of older adults, although the effect of physical activity, the number of comorbid disorders, and the number of total drugs the person was taking was significant. Given limited number of similar studies that assessed the impact of different GI medication on cognitive function of older adults, therefore this finding could not be compared with them.

Given the significant effect of PPIs on cognition, this finding is consistent with Makunts et al.'s study that described PPIs as drugs that are widely used over-the-counter and are considered safe. However, when the database of drug side effect reports was evaluated, the findings showed that a significant increase (OR= 3.29; 95% CI: 2.31 to 4.67) was observed in all types of memory disorders following the consumption of these drugs [11]. In Torres-Bondia cohort study, the correlation of proton pump inhibitor drugs with increased risk of Alzheimer's disease and non-Alzheimer's dementia was evaluated. The findings showed that PPI use was not associated with the risk of Alzheimer's disease (adjusted OR=1.06), although a slight increase in the incidence of non-Alzheimer's dementia was observed (adjusted OR=1.20). It was established that higher doses of PPIs were not associated with an increased risk of cognitive impairment, but individuals taking two types of PPIs had a higher incidence of Alzheimer's and non-Alzheimer's dementia than people taking one kind of PPI [13].

Contrariwise to our finding, Cooksey et al.' s cohort study in Wales, UK, reported a reduced dementia risk in older adults using PPIs [14]. Also, meta-analysis by Hussain et al. stated that the use of PPI drugs was not associated with the risk of dementia [29].

Our research showed a significant effect of drugs affecting GI tract movement on the cognitive function of senior adults. This category of GI medications includes different agents with different mechanisms of action. Some of them had anticholinergic properties, such as hyoscine or dicyclomine; while some act directly on the smooth muscles of GI tract to produce a bowel movement, such as bisacodyl. In recent years multiple longitudinal studies evaluated the impact of anticholinergic agents on cognitive function in old age [30-32]. Posis et al. showed that anticholinergic use correlated with lower neurocognitive performance; also, consumption of these drugs contributed to a faster decline in verbal fluency, learning, and global cognition [30]. Broder et al. reported that anticholinergic burden predicted worse cognitive function over time in late adulthood, especially in terms of executive function and episodic memory [31].

In the elderly, due to age-related changes such as changes in body composition and the function of various organs, the pharmacokinetics and pharmacodynamics of drugs are affected, and a precise and systematic approach should be taken to initiate and continue taking drugs, for example, the *"start low, go slow"* principle should be exercised [33].

Strengths and limitations

The most important strong point of this research is assessment of different categories of GI drugs and their effect on cognition in a large-scale community-based study of older adults. We did not conduct a structured psychiatric interview for the assessment of cognitive function in the participants. The latter can be mentioned as a limitation of our research. Although the case-control design of this research made it possible to compare the effect of GI drugs on the elderly with and without cognitive impairment, the longitudinal design of the study could have made a more accurate relationship between the consumption of these drugs and a cognitive function of older adults.

Recommendations for future studies

Longitudinal studies are needed to evaluate the long-term impact of different GI drugs on the cognitive function of older adults.

Practical implications and policymaking

Given high prevalence of GI medication (especially, PPIs and GI movement drugs) among senior adults, continuous screening of their cognitive function should be implemented by their caregivers.

Conclusion

Total intake of GI medications exhibited no statistically significant effect on the cognitive function of older adults. However, PPIs and drugs affecting GI tract movements caused a significant impact.

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Ethical approval and consent to participate

All participants (or their proxy respondents) gave a written informed consent prior to the beginning of the study.

The research protocol was approved by the Ethics Committee of Babol University of Medical Sciences, Iran, with the registration code IR.MUBABOL.HRI.REC.1400.212.

Conflict of Interests

The authors declare no conflicts of interest.

Availability of data and materials

The data are available from the corresponding author upon reasonable request.

Author contributions A.R.M., S.R.H., R.G., A.B. and S.M. conceived and designed the study. All authors were involved in data collection, analysis, and interpretation. S.R.H, A.B., R.G. and S.M. supervised the project. All authors contributed to the drafting and critical review of the manuscript and have approved the final draft of the manuscript prior to its publication.

Data reproducibility

The dataset presented in this study is available on request from the corresponding author during submission of the manuscript or after its publication.

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