American Journal of Gastroenterology
© 2008 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2008.02107.x

The Prevalence of Diarrhea and Its Association With Drug Use in Elderly Outpatients: A Multicenter Study

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OBJECTIVES: To evaluate the prevalence of diarrhea and its association with drug use in elderly outpatients.

METHODS: The study was carried out by 133 general practitioners (GPs) who referred to 24 geriatric units in Italy. The demographic data, disability, gastrointestinal symptoms, and current medications were evaluated using a structured interview, including the evaluation of the activities of daily living (ADL), the instrumental activities of daily living (IADL), and the gastrointestinal symptoms rating scale (GSRS).

RESULTS: The study included 5,387 elderly subjects who regularly completed the structured interview. In total, 488 patients (9.1% of the whole population, 210 men and 278 women, mean age 75.6 $\pm$ 6.2 yr, range 65–100 yr) reported diarrhea, that is, items 11 and 12 of the GSRS, during the 7-day period before the interview. The prevalence of diarrhea significantly increased with older age ($P = 0.025$), the severity of ADL ($P < 0.0001$) and IADL disability ($P < 0.0001$), and the number of drugs taken ($P = 0.0002$). A multivariate analysis demonstrated that the presence of diarrhea was significantly associated with the use of antibiotics (odds ratio [OR] 4.58, 95% confidence interval [CI] 1.95–10.73), proton pump inhibitors (OR 2.97, 95% CI 2.03–4.35), allopurinol (OR 2.19, 95% CI 1.26–3.81), psycholeptics (OR 1.82, 95% CI 1.26–2.61), selective serotonin reuptake inhibitors (OR 1.71, 95% CI 1.01–2.89), and angiotensin II receptor blockers (OR 1.46, 95% CI 1.08–1.99), also accounting for sex, age, and the use of antidiarrheal agents and drugs for functional gastrointestinal disorders.

CONCLUSION: Diarrhea is a common problem in elderly outpatients. Its prevalence increases with old age, the severity of disability, and the number of drugs. Monitoring the presence of diarrhea and its complications in elderly patients who need treatments with drugs significantly associated with diarrhea may be clinically useful.

(Am J Gastroenterol 2008;103:2816–2823)

INTRODUCTION

Epidemiological studies from western countries have reported that diarrhea is a common problem among people living in the community (1–5). The use of different study designs and definitions, however, made it difficult to compare the data from different studies, and therefore, to clarify whether older persons are predisposed to and/or are at a greater risk of acquiring diarrhea (6).

Clinical studies, however, reported that diarrhea in old age can significantly impair the quality of life and functional status of the affected individuals (7), and that it may be a significant cause of fecal incontinence (8), morbidity (9), and even mortality in the elderly (10).

Some studies have reported that in elderly subjects there is a significant association between diarrhea and drugs (11). No studies, however, have specifically explored the prevalence of diarrhea and its association with drug use in elderly outpatients.

As an early diagnosis and interventions are needed to prevent the severe consequences of diarrhea in the elderly, that is, dehydration, loss of electrolytes, and deterioration of nutritional status, it is important to know the prevalence of diarrhea and the use of those drugs that may be implicated in causing diarrhea in old age.

SOFIA Project Investigators (see Appendix)

The aim of the study was to evaluate the prevalence of diarrhea and its association with drug use in a large population of elderly outpatients.

METHODS

The study was funded by the FIRI (Fondazione Italiana Ricerca sull'Invecchiamento, Italian Foundation for the Research on Aging) and carried out by 133 general practitioners (GPs) in the frame of the SOFIA Project, that is, Observational Study on Drug Use by the Elderly (12).

At the study's conception, 192 GPs were randomly identified from local GP lists, 188 of whom attended a preliminary meeting to receive information about the aim, methods, and study design. The meeting was carried out by 24 educated specialists in geriatrics referring to 24 geriatric units in Italy. Of 188 GPs who attended the meeting, 133 agreed to carry out the investigation.

Inclusion Criteria

The investigation was conducted from March to June 2003. The GPs included all patients seen during a 2-wk period (10 working days) who agreed to participate in the study. All subjects aged 65 yr and over who sought their GP for a medical problem during this 2-wk period were included in the study. Elderly patients who were visited in their home or in nursing homes were not included.

Data Collection: Demographic and Clinical Variables

In all elderly subjects, the data were obtained by a structured interview of the patients and/or their relatives, and where possible, were confirmed by the GPs' medical records. The demographic data (age and gender), physical functions according to activities of daily living (ADL) (13) and instrumental activities of daily living (IADL) (14) questionnaires, current therapies, and gastrointestinal symptoms evaluated according to the gastrointestinal symptom rating scale (GSRS) (15) were recorded. Moreover, the number of gastroenterological visits and instrumental examinations related to the presence of disorders of the gastrointestinal tract, that is, gastrointestinal tract barium X-ray, colonoscopy, abdominal ultrasounds, and computerized tomography, which were carried out by patients during the last 6-month period, were recorded.

The records were computerized and e-mailed to the Statistics Reference Centre for evaluation.

Physical Function

The physical functions were assessed with standardized tests evaluating a patient's ability to perform six activities of daily living: bathing, dressing, transferring, walking, toileting, and eating (13). Eight instrumental activities of daily living—managing finances, taking medications, using the telephone, shopping for food or clothes, washing, using transportation, preparing meals, and doing housework—were also evaluated (14). According to previous studies (16), we defined severe disability as a loss of three or more functions on the ADL and/or IADL questionnaires, moderate disability as a loss of two functions on the ADL and/or IADL questionnaires, mild disability as a loss of at least one function on the ADL and/or IADL questionnaires, and no disability as no loss in ADL/IADL functions.

Gastrointestinal Symptom Rating Scale (GSRS)

To assess the gastrointestinal symptoms, we used the GSRS, a validated disease-specific questionnaire designed to evaluate common gastrointestinal symptoms. The GSRS includes 15 symptoms and uses a 7-point Likert scale in which 1 represents the most positive option and 7 the most negative. According to previous analyses (17), the severity of symptoms was graded as mild (1 and 2 points), moderate (3 and 4 points), and severe (5–7 points of Likert scale). The items are combined into five clinical syndromes: abdominal pain, reflux, indigestion, diarrhea, and constipation. Because the pathophysiology and clinical meaning of upper gastrointestinal symptoms differ from those of lower gastrointestinal symptoms, we evaluated the association between drug use and gastrointestinal symptoms separately for the upper and lower gastrointestinal tracts.

Data on the association between abdominal pain, reflux syndrome and indigestion syndrome (items 1–8 of the GSRS), and drug use have been published elsewhere (12). The items that explore the symptom constipation were (item 10) decreased passage of stools, (13) hard stools, and (15) defecation with straining and a feeling of incomplete evacuation of stools. The items including the symptom diarrhea in the GSRS are: (11) increased passage of stools, representing reported increased defecation; rate according to frequency, (12) loose stools representing reported loose or watery stool; rate according to consistency independent of frequency and feelings of incomplete evacuation, and (14) urgent need for defecation, representing reports of urgent need for defecation, feelings of incomplete control, and inability to control defecation; rate according to intensity, frequency, and impact on social performance.

According to the Rome diagnostic criteria for diarrhea (18), we included in the analysis patients who reported mild or moderate or severe discomfort in the items (11) and/or (12) of the GSRS, excluding patients who reported urgent need for defecation (item 14). The gastrointestinal symptoms reported by the patients were referred to the last week before the survey.

Drug Use

Drug use was identified according to the Anatomical Therapeutics Chemical (ATC) classification code system (19). In this system, drugs are divided into 14 main anatomical groups, each being further divided into two sublevels, therapeutic and pharmacological. During the interview, the names of specific drugs were recorded as well as the doses, the use patterns (acute, chronic, or on demand), and the duration of treatment. The patients were defined as drug users if they

were taking a drug from any of the above described classes at the time of the visit.

Statistical Analysis

The Pearson χ^2 test, the Student *t*-test for independent sample, and Fisher's exact test, when appropriate, were used for the comparison of the demographic and clinical characteristics and drug use in patients with diarrhea *versus* patients without gastrointestinal symptoms. The Cochrane Armitage trend test was used to evaluate the prevalence of diarrhea in patients with different age, grades of disability, and different number of drugs taken. The univariate analysis was performed to evaluate the potential correlations among sex, age, the use of individual drugs, and the presence of diarrhea. The binary logistic regression analyses were used to estimate the risk of diarrhea associated with medications, after adjusting for age, sex, and the use of drugs that resulted in the univariate analysis as significantly associated with diarrhea, that is, proton pump inhibitors (PPI), drugs for gastrointestinal disorders, antidiarrheal agents, iron salts, digoxin, angiotensin II receptor blockers (ARB), corticosteroids, l-thyroxin, antibiotics, nonsteroidal anti-inflammatory drugs (NSAID), allopurinol, psycholeptics, selective serotonin reuptake inhibitors (SSRI), and drugs for obstructive airway diseases.

The results are shown as odds ratios (OR) and relative 95% confidence intervals (CI) of the independent variables. The maximum likelihood method was used for entering and removing variables and for calculating variable interaction. A goodness-of-fit χ^2 test [$2 \times \ln$ (O/E)] was used to test the hypothesis that the final variable models fit the data adequately. The c-statistic was used to evaluate the usefulness of the model in predicting the response.

The statistical analysis was performed using the SPSS version 13.0 for Windows statistical software package. All *P* values were 2-tailed, with statistical significance indicated by a value of $P < 0.05$.

RESULTS

Prevalence of Diarrhea

During the study period, 5,533 subjects were observed by 133 GPs; 18 subjects were excluded because they did not fulfill the inclusion criteria (age 65 yr or over). Of the 5,515 elderly subjects who were eligible for the study, 5,387, that is, 97.7% (2,455 men and 2,932 women, mean age 75.1 ± 6.2 yr, range 65–100 yr), regularly completed the GSRS and were included in the final analysis. Of these subjects, 877 patients (16.3%, 357 men and 520 women; $P = 0.002$) reported abdominal pain, 764 patients (14.2%, 320 men and 444 women; $P = 0.027$) reported reflux syndrome, 1,388 patients (25.8%, 639 men and 699 women; $P = 0.067$) reported indigestion syndrome, and 1,288 patients (23.9%, 490 men and 798 women; $P < 0.0001$) reported constipation.

A total of 488 patients out of 5,387, that is, 9.1% of the total population, reported diarrhea, as evaluated according to the items 11 and 12 of the GSRS.

Table 1 shows the demographic and clinical characteristics of the study population divided according to the presence *versus* the absence of gastrointestinal symptoms. Patients with diarrhea were significantly older ($P = 0.004$) and more were women ($P = 0.046$) than patients without gastrointestinal symptoms. Patients with diarrhea, moreover, were significantly more disabled in both the ADL ($P < 0.0001$) and IADL ($P < 0.0001$). Patients with diarrhea were taking a significantly higher number of drugs than subjects without gastrointestinal symptoms ($P < 0.0001$). Moreover, patients with diarrhea had performed a significantly higher number of gastroenterological visits ($P < 0.0001$), barium X-ray

Table 1. Demographic, Functional, and Clinical Characteristics of Patients With Diarrhea and Without Gastrointestinal Symptoms

	Diarrhea (N = 488)	No GI symptoms (N = 1,569)	*P* Value
Women, N (%)	278 (57.0)	811 (51.7)	0.046
Age (yr)			
Mean ± SD	75.6 ± 6.2	74.4 ± 6.0	0.004
Range	65–100	65–99	–
Drug use (mean ± SD)	3.2 ± 2.0	2.4 ± 1.8	0.0001
Gastroenterological visits, N (%)	259 (53.1)	581 (37.0)	<0.0001
Gastrointestinal barium X-ray, N (%)	34 (7.0)	13 (0.8)	<0.0001
Colonoscopy, N (%)	50 (10.2)	25 (1.6)	<0.0001
Abdominal ultrasounds, N (%)	125 (25.6)	141 (9.0)	<0.0001
Abdominal computerized tomography, N (%)	26 (5.3)	23 (1.5)	<0.0001
ADL, N (%)*			
No disability	361 (74.0)	1418 (90.4)	
Mild disability	90 (18.4)	111 (7.1)	<0.0001
Moderate or severe disability	37 (7.6)	30 (2.6)	
IADL, N (%)†			
No disability	278 (57.0)	1130 (72.0)	
Mild disability	94 (19.3)	247 (15.7)	<0.0001
Moderate or severe disability	116 (23.8)	192 (12.2)	

*Activities of daily living.
†Instrumental activities of daily living.

Table 2. Prevalence of Diarrhea in 5,387 Patients According to the Individual Drug Treatment and Rates of Individual Drugs Used in Patients With Diarrhea and Patients Without Gastrointestinal Symptoms

ATC Code*	Drug/s	All Treated Patients N	Prevalence of Diarrhea N (%)	Drug Use in 488 Patients With Diarrhea N (%)	Drug Use in 1,569 Patients Without GI Symptoms N (%)	*P* Value
A02BA	H_2 antagonist receptors	97	5 (5.2)	5 (1.0)	11 (0.7)	0.544
A02BC	Proton pump inhibitors	562	69 (12.3)	69 (14.1)	68 (4.3)	<0.0001
A03	Drugs for functional gastrointestinal disorders	137	24 (17.5)	24 (4.9)	14 (0.9)	<0.0001
A05	Drugs for functional bile and liver therapy	37	5 (8.1)	5 (1.0)	6 (0.4)	0.145
A06	Laxatives	34	3 (8.8)	3 (0.6)	1 (0.1)	0.044
A07	Antidiarrheal agents	62	50 (80.6)	50 (10.2)	12 (0.8)	<0.0001
A10	Insulin- or oral blood glucose-lowering drugs	573	57 (9.9)	57 (11.7)	160 (10.2)	0.354
A11	Vitamin and mineral supplements	87	10 (11.5)	10 (2.0)	21 (1.3)	0.287
B01AA03	Warfarin	161	19 (11.8)	19 (3.9)	47 (3.0)	0.307
B01AC	Ticlopidine	203	22 (10.8)	22 (4.5)	51 (3.3)	0.207
B03A	Antianemic preparations of iron salts	23	6 (26.1)	6 (1.2)	5 (0.3)	0.026
B0A1C06/N02BA01	Low-dose aspirin	1,121	82 (7.3)	82 (16.4)	301 (19.2)	0.081
C01	Digoxin	359	36 (10.0)	36 (7.4)	77 (4.9)	0.041
C01DA	Nitrates	443	42 (9.5)	42 (8.6)	98 (6.2)	0.080
C02	Antiadrenergic agents	425	28 (6.6)	28 (5.7)	81 (5.2)	0.644
C03	Diuretics	753	69 (9.2)	69 (14.1)	180 (11.5)	0.131
C07	Beta-blockers	573	55 (9.6)	55 (11.3)	177 (11.3)	1.000
C08	Calcium channel blockers	1,205	104 (8.6)	104 (21.3)	330 (21.0)	0.899
C09	Agents acting on renin–angiotensin system inhibitors	1,745	157 (9.0)	157 (32.2)	513 (32.7)	0.868
C09C/C09D	Angiotensin II receptor blockers (ARB)	650	79 (12.2)	79 (16.2)	183 (11.7)	0.010
C10	Serum lipid-reducing agents	739	58 (7.8)	58 (11.9)	184 (11.7)	0.936
G04CA/G04CB	Urogenital system and sex hormones	448	40 (8.9)	40 (8.2)	127 (8.1)	0.925
H02	Corticosteroids	127	20 (15.7)	20 (4.1)	23 (1.5)	0.001
H03	Thyroid hormones l-thyroxin	210	25 (11.9)	25 (5.1)	49 (3.1)	0.050
I	Anti-infective drugs for systemic use	65	13 (20.0)	13 (2.7)	11 (0.7)	0.001
L	Antitumoral drugs and immunomodulators	142	8 (5.6)	8 (1.6)	34 (2.2)	0.584
M01A	NSAIDs	334	34 (10.2)	34 (7.0)	72 (4.6)	0.046
M01AH	Coxibs	155	15 (9.7)	15 (3.1)	39 (2.5)	0.516
M04	Allopurinol	182	24 (13.2)	24 (4.9)	38 (2.4)	0.009
M05BA	Bisphosphonates	210	21 (10.0)	21 (4.3)	42 (2.7)	0.072
N05	Psycholeptics	520	59 (11.3)	59 (12.1)	102 (6.5)	<0.0001
N06	Psychoanaleptics – SSRI	200	36 (18.0)	36 (7.4)	45 (2.9)	0.039
R03	Drugs for obstructive airway diseases	297	31 (10.4)	31 (6.4)	71 (4.5)	0.090

*Anatomical Therapeutic Chemical classification.

($P < 0.0001$), colonoscopies ($P < 0.0001$), abdominal ultrasounds ($P < 0.0001$), and computerized tomography of the abdomen ($P < 0.0001$) than patients without gastrointestinal symptoms.

No difference was found in the prevalence of diarrhea between men and women (8.6% *vs* 9.5% respectively; $P = 0.282$).

The prevalence of diarrhea significantly increased with advancing age (8.3% of diarrhea in patients aged 65–74 yr, 9.9% in patients aged 75–84 yr, 11.0% in patients aged $\geq$ 85 yr; $P = 0.025$). Moreover, the prevalence of diarrhea significantly increased with the severity of disability evaluated by ADL (8.1% of diarrhea in patients without disability, 13.9% in patients with mild disability, 15.9% in patients with moderate disability, and 15.3% in patients with severe disability; $P < 0.0001$) and IADL (8.2% of diarrhea in patients without disability, 9.4% in patients with mild disability, 9.9% in patients with moderate disability, and 11.0% in patients with severe disability; $P < 0.0001$).

Diarrhea and Drug Use

A significantly higher prevalence of diarrhea was observed in patients who were taking a higher number of drugs (6.8% for 0 drugs, 8.2% for 1–2 drugs, 11.0% for 3–5 drugs, and 11.7% for $\geq$ 6 drugs; $P < 0.0002$).

Table 2 shows the prevalence of diarrhea in patients divided according to the drugs taken. As expected, a high use of antidiarrheal drugs was observed in patients with diarrhea (80.6%). Considering the other drug classes, the highest prevalence of diarrhea was observed in patients who were taking iron salts (26.1%), antibiotics (20.0%), SSRIs (18.0%), drugs for functional gastrointestinal disorders (17.5%), and steroids (15.7%). Compared to the mean value of prevalence observed in the study population (9.1%), a higher rate of diarrhea was also observed in patients who were taking allopurinol (13.2%), PPI (12.3%), ARB (12.2%), thyroid hormones l-thyroxin (11.9%), warfarin (11.8%), psycholeptics (11.3%), ticlopidine (10.8%), NSAID (10.2%), bisphosphonates (10.0%), and digoxin (10.0%).

Table 3. Risk of Diarrhea in Elderly Outpatients According to Drug Use

Drug Class	OR	95% CI	*P* Value
Overall diarrhea			
Antidiarrheal agents	13.28	6.88–25.64	<0.0001
Antibiotics	4.58	1.95–10.73	<0.0001
Drugs for functional gastrointestinal disorders	4.44	2.19–9.02	<0.0001
Proton pump inhibitors	2.97	2.03–4.35	<0.0001
Allopurinol	2.19	1.26–3.81	0.006
Psycholeptics	1.81	1.26–2.61	0.001
Selective serotonin reuptake inhibitors	1.71	1.01–2.89	0.045
Angiotensin II receptor blockers	1.46	1.08–1.99	0.015
Moderate-to-severe diarrhea			
Antidiarrheal agents	30.53	15.03–61.99	<0.0001
Drugs for functional gastrointestinal disorders	5.68	2.35–13.71	<0.0001
Antibiotics	5.32	1.68–16.77	0.004
Proton pump inhibitors	3.63	2.14–6.17	<0.0001
Selective serotonin reuptake inhibitors	2.44	1.19–5.04	0.016
L-thyroxin	2.15	1.01–4.57	0.047
Angiotensin II receptor blockers	2.01	1.29–3.12	0.002

Table 2 shows the percentages of individual drugs taken by patients with diarrhea *versus* patients without gastrointestinal symptoms. In patients with diarrhea, a significantly higher use of antidiarrheal agents (OR 14.81, 95% CI 7.82–28.06), drugs for functional gastrointestinal disorders (OR 5.75, 95% CI 2.95–11.20), iron salts (OR 3.89, 95% CI 1.18–12.81), anti-infective drugs for systemic use (OR 3.88, 95% CI 1.73–8.71), PPI (OR 3.64, 95% CI 2.56–5.17), steroids (OR 2.87, 95% CI 1.56–5.28), allopurinol (OR 2.08, 95% CI 1.24–3.51), psycholeptics (OR 1.98, 95% CI 1.41–2.77), SSRI (OR 1.98, 95% CI 1.22–3.23), l-thyroxin (OR 1.67, 95% CI 1.01–2.74), NSAID (OR 1.56, 95% CI 1.02–2.37), digoxin (OR 1.54, 95% CI 1.02–2.32), and ARB (OR 1.46, 95% CI 1.10–1.95), than patients without gastrointestinal symptoms, was observed.

Dividing patients according to the severity of diarrhea, we observed that digoxin, NSAIDs, allopurinol, and psycholeptics were significantly associated with mild diarrhea, while antidiarrheal agents (OR 33.36, 95% CI 16.97–65.58), drugs for functional gastrointestinal disorders (OR 8.86, 95% CI 4.09–19.17), iron salts (OR 5.42, 95% CI 1.29–22.89), antibiotics (OR 5.00, 95% CI 1.83–13.69), PPI (OR 4.91, 95% CI 3.12–7.62), steroids (OR 4.48, 95% CI 2.15–9.36), SSRI (OR 2.48, 95% CI 1.28–4.78), drugs for obstructive airway diseases (OR 2.11, 95% CI 1.20–3.72), l-thyroxin (OR 2.07, 95% CI 1.05–4.06), and ARB (OR 1.88, 95% CI 1.26–2.81) were significantly associated with the presence of moderate or severe grade of diarrhea.

As shown in Table 3, the multivariable analysis demonstrated that the presence of diarrhea was significantly associated with the use of antibiotics, PPI, allopurinol, psycholeptics, SSRI, and ARB, also accounting for sex, age, and the use of antidiarrheal agents and drugs for functional gastrointestinal disorders. Considering only patients with moderate or severe diarrhea, a significant association was observed with the use of antibiotics, PPI, SSRI, l-thyroxin, and ARB. The c-statistic was 0.68 (95% CI 0.651–0.708) for overall diarrhea and 0.73 (95% CI 0.680–0.772) for the moderate-to-severe diarrhea, confirming the usefulness of the model in predicting the response.

DISCUSSION

Some studies have explored the prevalence of diarrhea in old age, but the data do not give homogeneous results. The differences in the definitions of diarrhea and the methodology of the study recruitment may explain the discrepancies in the results. In our study, the evaluation of gastrointestinal symptoms was ascertained by the physician who carried out a structured interview of patients. Diarrhea was defined in agreement with the Rome diagnostic criteria (18) as the increased frequency of stools and/or the presence of loose or watery stool, that is, the items 11 and 12 of the GSRS. Thus, the prevalence of diarrhea that we found in our population of elderly outpatients was 9.1%. This rate is apparently lower than the 14.9% of prevalence of diarrhea reported in a previous study performed in 328 noninstitutionalized elderly subjects from the United States (1). In this study, the collection of data was made through a mailed self-administered questionnaire, and the patients with diarrhea included in the survey were both "the subjects with a stool frequency more than three stools per days" and "the subjects who passed loose or watery stool and/or with urgent need for defecation," that is, items 11, 12, and 14 of the GSRS. Indeed, in our population, if we define as patients with diarrhea all patients who reported a positive answer in the items 11, 12, and 14, the prevalence of diarrhea was 13.9%, that is, very similar to the rate reported by Talley *et al*. (1). More recently, a cross-sectional survey carried out in Australia, Canada, Ireland, and the United States reported a prevalence of diarrhea of 3.9% in elderly subjects aged 65 yr or more (2). In this study, diarrhea was defined as three loose stools or bowel movements in any 24-h period during the 4 wk before the interview. In the study, however, data were collected by a telephone call,

thus excluding persons who do not have access to a fixed line telephone in their home, and therefore, probably the older and more disabled elderly people. This could explain the low prevalence of diarrhea found in that survey.

In our study, we observed that the prevalence of diarrhea significantly increases with increasing of both the age and the grade of disability, as evaluated by the ADL and the IADL.

Moreover, we demonstrated that, in the past 6 months, elderly patients with diarrhea underwent a significantly higher number of gastroenterological visits and instrumental examinations of the gastrointestinal tract such as barium X-ray, colonoscopies, abdominal ultrasounds, and computerized tomographies than elderly subjects without gastrointestinal symptoms. This finding is indirectly in agreement with previous studies supporting the concept that diarrhea in old age may significantly impair the quality of life and functional status of the affected individuals (3, 7), and that it may be a cause of morbidity (9) and complications (6), leading to a severe burden in hospitalized elderly patients (20).

Diarrhea is a relatively frequent adverse event, accounting for about 7% of all drug-adverse effects (21). Our study demonstrates that elderly patients with diarrhea were taking a significantly higher number of drugs than patients without gastrointestinal symptoms; moreover, a significant increase in the prevalence of diarrhea occurred in patients who were treated with a progressively higher number of drugs, reaching a prevalence of 11.0% in patients who were taking 3–5 drugs, and a prevalence of 11.7% in patients who were concomitantly taking 6 or more drugs.

More than 700 drugs have been implicated in causing diarrhea. In this elderly population of outpatients, the drugs significantly associated with the presence of diarrhea, other than antidiarrheal agents, were antimicrobials, PPI, allopurinol, psycholeptics, SSRI, and ARB. Several mechanisms have been reported to be involved in inducing drug-related diarrhea such as altered gastrointestinal defenses, mucosal damage of the small and large intestine, and/or disruption of normal pathophysiological processes of fluid and electrolyte absorption and secretion; sometimes, more than one mechanism may be involved (22).

Antibiotic-associated diarrhea is a common adverse event of antibiotic therapy. In agreement with previous findings (23), we found a prevalence of 20% of diarrhea in patients who were treated with antibiotics. Therapy with antibiotics, especially broad-spectrum agents, may affect the normal intestinal microflora, with the consequence of increasing the risk of proliferation of pathogenic microorganisms such as *Clostridium difficile* (*C. difficile*) (24). As laboratory data and/or the results of stool cultures were not collected, from the findings of our study, we cannot know the prevalence of *C. difficile* infection and/or other bacterial pathogens in patients with antibiotic-associated diarrhea.

In this study, a significant association between PPI use and diarrhea was found. A case report study suggested that PPIs, particularly lansoprazole, could lead to either lymphocytic or collagenous colitis (25). More recently, PPI use has been associated with *C. difficile* diarrhea among hospital inpatients (26) as well as with community-acquired *C. difficile* colitis (27). This finding is in agreement with a previous epidemiological study carried out in a population of over 10 thousand lansoprazole users reporting that the concomitant use of lansoprazole and oral antibiotics significantly increases the risk of diarrhea (28). In our study, no differences were found in the prevalence of diarrhea between the different individual PPIs as well as between PPI plus antibiotics *versus* PPI alone.

In agreement with previous data, allopurinol (29), psycholeptics (6), and SSRI (30) were significantly associated with diarrhea in our population. The mechanisms through which these drugs may cause diarrhea are still unknown. Probably, both motility and inflammatory mechanisms may be involved. Indeed, SSRIs may induce an increase in the intestinal release of serotonin (31), a well-known modulator of intestinal function that increases gastrointestinal motility (32) and has been implicated in the pathophysiology of diarrhea associated with inflammatory diseases (33). Recently, a significant association between the use of SSRI, specifically sertraline, and a microscopic colitis was also reported (34). In our study, no significant differences in the association with diarrhea were observed among fluoxetine, citalopram, paroxetine, and sertraline.

In the study, a significant association between the use of ARB and diarrhea was found. Up to now, there are no studies that explored the mechanisms that may be involved in causing diarrhea by this class of drugs. The Micromedex healthcare series report that 2–3% of patients treated with losartan, irbesartan, and valsartan had diarrhea (35). No diarrhea was reported with the use of candesartan, telmisartan, eprosartan, and olmesartan. In our study, the prevalence of diarrhea in patients who were taking ARB was 12.2% and the individual drugs implicated were losartan, irbesartan, valsartarn, candesartan, and telmisartan.

In conclusion, diarrhea is a common problem in elderly outpatients. Its prevalence increases with old age, the severity of disability, and the number of drugs taken. Specific classes of drugs are significantly associated with diarrhea, including antibiotics, PPI, allopurinol, psycholeptics, SSRI, and ARB. Monitoring the presence of diarrhea and its complications in elderly patients who need to be treated with these drugs may be clinically useful.

APPENDIX

The SOFIA Project Investigators

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ACKNOWLEDGMENTS

This work was supported by grants from Ministero della Salute, IRCCS Research Program 2006-2008, Line 2: "Malattie di rilevanza sociale."

STUDY HIGHLIGHTS

What Is Current Knowledge

- Diarrhea can significantly impair the quality of life and functional status in old age and may be a cause of morbidity and mortality.
- No large epidemiological studies have explored the prevalence of diarrhea in elderly outpatients and its association with drug use in Italy.

What Is New Here

- This is a large epidemiological study on elderly outpatients evaluating the prevalence of diarrhea and the risk of diarrhea associated with drug use.
- The prevalence of diarrhea increases with old age, the severity of disability, and the number of drugs.
- The use of antibiotics, proton pump inhibitors, allopurinol, psycholeptics, selective serotonin reuptake inhibitors, and angiotensin II receptor blockers is significantly associated with diarrhea in elderly outpatients.

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Received February 21, 2008; accepted June 8, 2008.

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CONFLICT OF INTEREST

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Specific author contributions: Alberto Pilotto, Marilisa Franceschi, Francesco Di Mario, and Franco Rengo participated in the study concept and design, interpretation of data, data analysis, and preparation of manuscript. Dino Vitale participated in the study concept and design, interpretation of data, and statistical analysis. Augusto Zaninelli and Davide Seripa participated in the study concept and design and interpretation of data. All authors participated in discussing the results and critical revision of the manuscript. The SOFIA Project Investigators selected patients and collected data.

Financial support: This study was supported by a grant from the "Ministero della Salute," IRCCS Research Program, Ricerca Corrente 2006-2008, Linea n. 2 "Malattie di rilevanza sociale," and Fondazione Italiana per la Ricerca sull'Invechiamento (FIRI), Florence, Italy.

Potential competing interests: None.