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Pattern of psychotropic medications use in a cohort of patients with uninvestigated dyspepsia undergoing upper endoscopy

A retrospective study

Maria Pina Dore, MD, PhD[a,b,*], Laura Piras, MD[a], Liliana Lorettu, MD[a], Giovanni Mario Pes, MD, PhD[a]

Abstract

The prevalence of psychotropic drugs usage is growing in the general population. Moreover, patients with dyspeptic symptoms are increasingly referred to the use of psychiatric and antianxiety drugs in addition to the primary medical treatment. The focus of this observational retrospective study was to investigate the burden of psychotropic drugs usage in a cohort of patients with uninvestigated dyspepsia scheduled for esophagogastroduodenoscopy.

Medical records of 11,275 patients (4377 men and 6898 women, age range 18–96 years) referred to the Gastroenterology Unit of the University of Sassari, Sardinia, between January 1995 and December 2013 were reviewed. Information regarding any taken medications including psychiatric and antianxiety drugs was collected. Age- and gender-specific frequency of drug usage was calculated, and their association with marital status, smoking habits, place of residence, socioeconomical status, and polypharmacy was investigated by multiple logistic regression analysis.

Psychiatric drugs usage was detected in 531 out of 11,275 (4.7%) patients, with preponderance of women (6.1% vs 2.6%, $P <$ 0.0001). The most prescribed drug categories were selective serotonin-reuptake inhibitors and tricyclic antidepressants.

The frequency of antianxiety medication use was 9.8% (1009/11,275) and increased with aging, whereas psychiatric drugs reached the plateau in the fifth decade. The cohort effect was remarkable for psychiatric drugs usage in patients born after 1950 compared to those born before (odds ratio: 1.47), whereas it was absent for antianxiety drugs. Conditions significantly associated with psychotropic drugs usage were assumption of more than 2 nonpsychotropic drugs, aging, female gender, smoking, marriage, widowhood, divorce, and socioeconomic status. In contrast, place of residence did not increase the consumption of psychotropic drugs. The influence of marriage and widowhood disappeared after adjusting for all covariates.

Our study confirmed the frequent use of psychotropic medications with uninvestigated dyspepsia. However, the pattern of consumption was different for antianxiety and psychiatric drugs.

Abbreviations: CI = confidence interval, NaSSAs = noradrenergic and specific serotonergic antidepressants, OR = odds ratio, SNRIs = serotonine and norepinephrine-reuptake inhibitors, SSRIs = selective serotonin-reuptake inhibitors, TCAs = tricyclic antidepressants.

Keywords: antianxiety, cohort effect, dyspepsia, psychiatric drugs

1. Introduction

Dyspepsia is a syndrome characterized by a miscellanea of symptoms related to the upper gastrointestinal tract. In developed countries, approximately 25% of individuals complain dyspeptic symptoms each year.[1] In the majority of patients an underlying organic disease is absent, and in these cases dyspepsia is defined as functional or idiopathic. The syndrome is one of the most frequent reason for consulting in primary care.[2] In order to simplify the management of patients, dyspeptic symptoms have been classified into 3 groups by a consensus of experts[3]: *ulcer-like dyspepsia*, where the predominant symptom is pain centered in the epigastric region; *dysmotility-like dyspepsia*, associated with upper abdominal fullness, early satiety, bloating, or nausea; and *unspecified (nonspecific) dyspepsia* when symptoms do not fulfill the criteria for *ulcer-* or *dysmotility-like dyspepsia*.[3] In presence of so-called alarm-features, that is, signs or symptoms suggestive of a severe organic disease, patients are usually recommended to undergo invasive procedures, and especially esophagogastroduodenoscopy as a first diagnostic line.[1–4] However, functional gastrointestinal disorders are prevalent in the general population, and conducive to reduced quality of life as well as elevated healthcare costs due to increased prescription of medications, hospitalizations, and workplace absenteeism.

There is general consensus about the existence of a strong psychosomatic component in the physiopathology of functional dyspepsia (FD). Particularly, the role of stressful psychosocial factors acting in developed societies have long been identified as potential triggers.[5,6] As a result of improved diagnostic skills,

the incidence and prevalence of FD in the general population have grown in the last decades, and patients are increasingly referred to therapeutic strategies including psychotherapy and use of psychiatric and/or antianxiety drugs in addition to the primary medical treatment.[7,8] In North America, the prevalence of FD in the general population is estimated to be around 13%.[9] Similarly, in Europe, including Italy, a prevalence in the range of 11 to 15% was observed.[10,11] A small number of intervention studies attempting to investigate the effectiveness of antidepressant drugs[5] showed a clear benefit in the treatment of FD, especially in the long term. However, the superiority of this approach over conventional treatment using antacids, proton pump inhibitors, and eradication of *Helicobacter pylori* remains largely unproven.[4,12] A special attention has been addressed in elderly patients, since in old age the presence of FD may exacerbate a pre-existing depression and in turn may contribute to the overall worsening of life quality. Moreover, prescription of psychotropic drugs in the elderly may pose problems of serious side effects that should be avoided by carefully selecting the most appropriate type and dosing of medications. However, the extent of the problem concerning psychotropic medications use in dyspeptic patients is not well known.[13]

Focus of this study was to explore the association between uninvestigated dyspepsia and use of psychotropic drugs in a large cohort of patients from Northern Sardinia undergoing upper endoscopy.

2. Materials and methods

2.1. Study population

Clinical records of patients complaining dyspeptic symptoms and scheduled for upper endoscopy to a tertiary GI clinic, University of Sassari, Northern Sardinia, from January 1995 to December 2013 were collected. Demographic data including gender and age were available. In addition, information such as place of residence (rural or urban), marital status, smoking habits, adult occupation, and a detailed list of taken medications (prescribed and over the counter), 2 months before the interview were retrieved. Patients did not undergo psychiatric evaluation. A part of the same database was recently utilized for a number of retrospective, observational, and epidemiological studies.[14,15]

2.2. Ethical considerations

An Institutional Review Board approval was obtained from the local ethics committee: *Comitato di Bioetica, Azienda Ospedaliero Universitaria di Sassari*, Italy (Prot No. 2099/CE, 2014).

2.3. Statistical analysis

Psychotropic drugs usage by patients with uninvestigated dyspepsia was the primary outcome variable in this study. Patients were stratified according to gender and decades of age. Binary variables were created to code the patients' place of residence (0, "urban" and 1, "rural") and smoking habits (0, "never smoker" and 1, "former or current smoker"). Marital status of each patient, originally expressed as "single", "married", "widow", and "divorced" in the charts, was recoded into an ordinal variable ranging from 1 to 4. Current or past (before retirement) patient's occupation, was used as a surrogate of social economic status and were clustered into 4 categories in descending order. Psychiatric medications were classified into tricyclic antidepressants (TCAs), monoamino-oxidase inhibitors,

selective serotonin-reuptake inhibitors (SSRIs), serotonine and norepinephrine-reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants, norepinephrine reuptake inhibitors, and atypical antidepressants. In addition, use of antianxiety medications was included in the analysis. The use of each drug was expressed as a binary variable: 0 = no use and 1 = use. The overall point prevalence was calculated as the total number of taken drugs. For the interpretation of data, it was assumed that psychotropic drugs were proxy for the presence of psychiatric and/or anxiety disorders. Furthermore, polypharmacy was evaluated as the number of different medications (other than psychiatric and antianxiety), taken by patients for any additional disease. The association between psychiatric and antianxiety drugs assumption and demographic or clinical variables was measured as unadjusted odds ratio (OR) and their 95% confidence intervals (CIs). In addition, the probability to take psychiatric drugs and tranquillizers was tested by using a multiple logistic regression model. The use of drugs in the current therapy was selected as dependent variable, while gender, age, marital status, place of residence, smoking habits, occupation, and polypharmacy were included as independent (explanatory) variables. For each covariate, the regression coefficients and their standard error (SE) were calculated as well as the ORs and their 95% CIs using the Wald formula (95% CI = $OR^{1 \pm \text{ß/SE}}$). Adjusted R^2 statistic was used to assess model fit. All statistical analyses were performed using SPSS statistical software (version 16.0, Chicago, IL). P values <0.05 were considered statistically significant.

3. Results

A total of 11,275 clinical records were available for the analysis (Table 1). The proportion of women was preponderant 61.2% (6898/11,275). Mean age at the time of endoscopic procedure was 52.7 ± 17.2 years among men and 50.1 ± 17.5 years among women.

Overall, the use of psychiatric drugs was recorded in 531 patients (4.7%) with a bias toward women (F: 6.1% vs M: 2.6%) (Table 1). Use of antianxiety drugs was 9.8% (1109/11,275) and significantly associated with aging, female gender, smoking habits, marriage, widowhood, and divorce, belonging to the middle social class, and polypharmacy (Table 2). The proportion of patients under antianxiety treatment and psychiatric drugs according to pharmaceutical classes is displayed in Fig. 1. SSRIs were the most common (3.4%) antidepressant type, followed by TCAs (0.6%), SNRIs (0.4%), and Atypical (0.3%), while the consumption of other classes was negligible. The distribution of psychiatric medications use according to patient age and gender is shown in Fig. 2. Women displayed a peak of usage in the fifth decade, reaching a plateau thereafter. Among men, the drug use increased progressively according to aging, although was lower compared to women in each decade. Fig. 3 shows the use of antianxiety and psychiatric drugs according to decades. Interestingly, the trend of antianxiety and psychiatric drugs usage was not similar, antianxiety use rose according to aging, while psychiatric drugs use reached the plateau in the fourth decade.

Since dyspepsia is more prevalent in industrialized countries and Sardinian population underwent a sociocultural transition between 1950 and 1960, in order to test the cohort effect, more specific analyses were done. Patients 50 to 69 years old were stratified according to the birth cohort (born before or after 1950) and compared for the psychotropic medications use. The

Table 1

Proportion of subjects taking psychiatric drugs among 11,275 patients with uninvestigated dyspepsia according to studied variables.

Variables	Total dyspeptic patients no.	Patients taking psychiatric drugs			Patients taking antianxiety drugs		
		Number, %	Unadjusted ORs* (95% CI†)	P	Number, %	Unadjusted ORs* (95% CI†)	P
Age							
<20	273	4 (1.5)	Reference	–	5 (1.8)	Reference	–
20–29	1294	32 (2.5)	2.97 (1.05–8.45)	**0.032**	42 (3.2)	1.80 (0.70–4.59)	0.213
30–39	1697	55 (3.2)	3.93 (1.42–10.89)	**0.005**	108 (6.4)	3.64 (1.47–9.01)	**0.003**
40–49	1825	106 (5.8)	7.23 (2.65–19.72)	**<0.0001**	178 (9.8)	5.79 (2.36–14.22)	**<0.0001**
50–59	2112	113 (5.4)	6.63 (2.43–18.06)	**<0.0001**	250 (11.8)	7.20 (2.94–17.60)	**<0.0001**
60–69	2219	117 (5.3)	6.18 (2.27–16.83)	**<0.0001**	279 (12.6)	7.71 (3.15–18.84)	**<0.0001**
70–79	1429	76 (5.3)	6.24 (2.27–17.14)	**<0.0001**	188 (13.2)	8.12 (3.31–19.93)	**<0.0001**
≥80	426	28 (6.5)	7.71 (2.68–22.15)	**<0.0001**	59 (13.8)	8.62 (3.41–21.76)	**<0.0001**
Gender							
Men	4377	113 (2.6)	Reference	–	282 (6.4)	Reference	–
Women	6898	418 (6.1)	2.43 (1.97–3.01)	**<0.0001**	827 (12.0)	1.98 (1.72–2.28)	**<0.0001**
Residence area							
Urban	5912	292 (4.9)	Reference	–	558 (9.4)	Reference	–
Rural	5363	239 (4.5)	0.90 (0.75–1.07)	0.227	551 (10.3)	1.10 (0.97–1.24)	0.137
Smoking habits							
No smoker	8260	505 (6.1)	Reference	–	772 (9.3)	Reference	–
Smoker	3015	238 (7.8)	1.32 (1.13–1.55)	**0.0006**	337 (11.2)	1.22 (1.07–1.40)	**0.004**
Marital status							
Single	3150	100 (3.2)	Reference	–	214 (6.8)	Reference	–
Married	6929	343 (3.4)	1.59 (1.27–1.99)	**0.0001**	699 (10.1)	1.54 (1.31–1.81)	**<0.0001**
Widow	890	57 (6.6)	2.09 (1.49–2.92)	**<0.0001**	146 (16.4)	2.69 (2.15–3.37)	**<0.0001**
Divorced	306	31 (11.0)	3.44 (2.26–5.24)	**<0.0001**	50 (16.3)	2.68 (1.92–3.74)	**<0.0001**
Socioeconomic status							
I class	1066	53 (5.0)	Reference	–	99 (9.3)	Reference	–
II class	2754	116 (4.2)	0.84 (0.60–1.17)	0.306	181 (6.6)	0.69 (0.53–0.89)	**0.004**
III class	3940	152 (3.9)	0.77 (0.56–1.06)	0.103	295 (7.5)	0.79 (0.62–1.00)	0.053
IV class	4958	329 (6.6)	1.36 (1.01–1.83)	**0.043**	526 (10.6)	1.16 (0.93–1.45)	0.199
Polypharmacy							
No drug	4105	123 (3.0)	Reference	–	255 (6.2)	Reference	–
1–3 drugs	6134	281 (4.6)	1.55 (1.25–1.93)	**0.0001**	652 (10.6)	1.80 (1.54–2.09)	**<0.0001**
>3 drugs	1036	127 (12.3)	4.52 (3.49–5.86)	**<0.0001**	202 (19.5)	3.66 (3.00–4.46)	**<0.0001**

* Odds ratio.
† Confidence interval.
Bold numbers are statistically significant.

psychiatric drug usage was higher in those born after 1950 than those born before: 67/964 (7.0%) versus 163/3367 (4.8%), OR: 1.47 (95% CI 1.09–1.97); P=0.010. In contrast, the pattern of tranquillizers use did not differ in patients 50 to 69 years old born before 1950: 406/3367 (12.0%); and after 1950: 123/964 (12.7%), OR: 1.07 (95% CI 0.86–1.32); P=0.558.

The risk of taking psychotropic drugs was expressed by unadjusted (Table 1) and adjusted (Table 2) ORs for each covariate. Variables associated with an increased risk were similar for both antidepressants and tranquillizers and included —in order of magnitude—aging, polypharmacy, female gender, marriage, widowhood, divorce, and smoke, whereas place of residence did not show association. Low socioeconomic status was significantly associated with psychiatric use, whereas antianxiety drugs were significantly more used in the middle class (Table 1). Aging and female gender remained significantly associated with psychotropic drugs consumption, also after adjustment by multivariate regression (Table 2). Polypharmacy was strongly related to the use of psychiatric medications: patients taking 1 to 3 drugs or more than 3 drugs showed an increased risk of taking psychotropic medications. Assuming that polypharmacy was a proxy for comorbidities, the highest number of treatments taken was the strongest predictive factor associated with the use of psychiatric and antianxiety medi-

cations. Among current or former smokers, the risk of assuming psychiatric drugs or tranquillizers was increased for both. The status of widow or married was not anymore a risk for psychotropic medications usage after adjusting for all covariates. Interestingly, the effect of social economic status remained for antianxiety consumption but was absent for psychiatric drugs use (Table 2).

4. Discussion and conclusion

FD is considered a gastrointestinal disorder characterized by *H. pylori* infection, gastric motility disorders, visceral hypersensitivity given by a lower threshold for pain in patients with a normal gastric compliance and disbiosis of gastrointestinal microbiome.[16–20] Presence of dyspeptic symptoms is also associated with somatization, generalized anxiety disorder, depression, and abuse in childhood.[21,22] Despite intensive research, the causes of this disorder remain elusive, or rather, complicated by the interaction of many heterogeneous factors. Dyspeptic chronic symptoms often disturb the individual life worsening anxiety and depression.[23] Patients in such mental state tend to complain of their FD symptoms as being more severe than other patients.[24] Moreover, in clinical practice, treatment of FD is not always satisfactory, and because of that a

Table 2

Proportion of subjects taking antianxiety drugs among 11,275 patients with uninvestigated dyspepsia according to studied variables.

Variables	Patients taking psychiatric drugs			Patients taking antianxiety drugs		
	Adjusted ORs[*]	95% CI[†]	P	Adjusted ORs[*]	95% CI	P
Age						
<20	Reference		–	Reference		–
20–29	1.789	0.622–5.141	0.280	1.911	0.745–4.903	0.178
30–39	2.265	0.793–6.470	0.127	4.482	1.791–11.215	**0.001**
40–49	3.724	1.310–10.589	**0.014**	6.932	2.775–17.317	**<0.0001**
50–59	4.053	1.426–11.525	**0.009**	8.213	3.292–20.494	**<0.0001**
60–69	3.558	1.252–10.112	**0.017**	8.392	3.365–20.928	**<0.0001**
70–79	2.934	1.021–8.432	**0.046**	7.637	3.044–19.160	**<0.0001**
≥80	3.651	1.205–11.061	**0.022**	7.827	3.017–20.303	**<0.0001**
Gender						
Men	Reference		–	Reference		–
Women	2.560	2.060–3.180	**<0.0001**	2.560	2.060–3.180	**<0.0001**
Residence area						
Urban	Reference		–	Reference		–
Rural	0.902	0.755–1.078	0.257	1.087	0.956–1.237	0.204
Smoking habits						
No smoker	Reference		–	Reference		–
Smoker	2.196	1.675–3.050	**<0.0001**	1.362	1.110–1.672	**<0.0001**
Marital status						
Single	Reference		–	Reference		–
Married	1.169	0.902–1.516	0.238	0.903	0.753–1.083	0.271
Widow	1.087	0.739–1.599	0.671	1.101	0.847–1.430	0.472
Divorced	2.356	1.507–3.683	**<0.0001**	1.715	1.210–2.432	**0.002**
Socioeconomic status						
I class	Reference		–	Reference		–
II class	1.06	0.62–1.82	0.831	0.736	0.566–0.958	**0.023**
III class	1.25	0.73–2.14	0.405	0.897	0.695–1.158	0.404
IV class	1.53	0.93–2.51	**0.096**	1.108	0.874–1.406	0.396
Polypharmacy						
No drug	Reference			Reference		
1–3 drugs	1.399	1.123–1.743	**0.003**	1.496	1.282–1.746	**<0.0001**
>3 drugs	4.309	3.254–5.706	**<0.0001**	2.749	2.219–3.405	**<0.0001**

[*] Odds ratio.
[†] Confidence interval.
Bold values are statistically significant.

number of patients try to seek relief by turning to empirical or nonpharmacological therapies, whose effectiveness is quite dubious.[25]
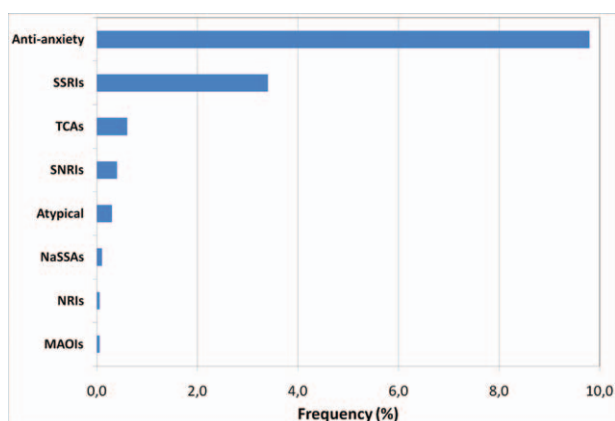

Figure 1. Prevalence of psychotropic drugs used among 11,275 dyspeptic patients according to medication classified as antianxiety medications, selective serotonin-reuptake inhibitors, tricyclic antidepressants, serotonin and norepinephrine-reuptake inhibitors, atypical antidepressants, noradrenergic and specific serotonergic antidepressants, norepinephrine reuptake inhibitors, and monoamino-oxidase inhibitors.

Recently, a strong biopsychosocial influence has been hypothesized in this disorder, and this view is increasingly influencing medical decisions regarding a more rational treatment and clinical management.[26] Often, it is difficult in clinical practice to ascertain a cause–effect relationship or whether the psychological impairment is a mere consequence of FD. In the last
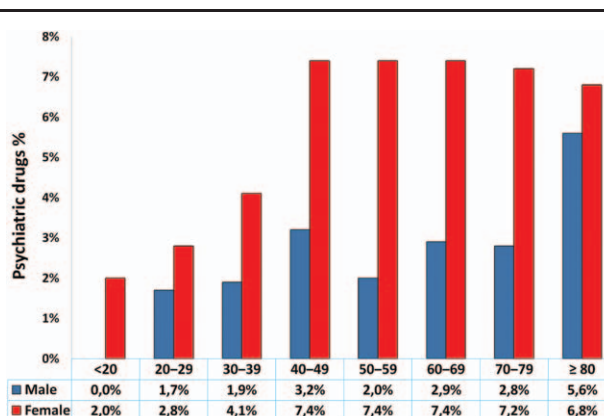

Figure 2. Cumulative frequency of psychiatric drugs use in 11,275 dyspeptic patients by age decade and gender.
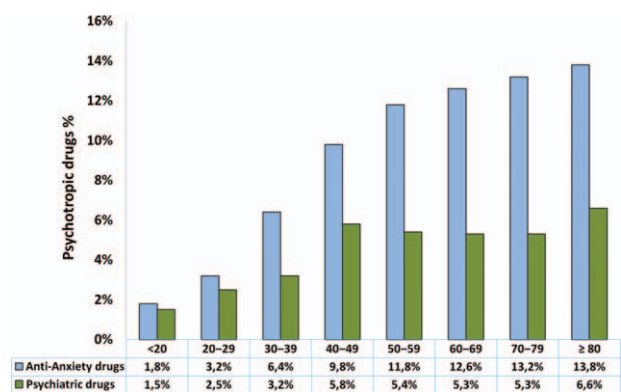
Figure 3. Frequency of antianxiety and psychiatric drugs use in dyspeptic patients by age decade.

decades, the use of psychiatric and/or antianxiety drugs in FD has dramatically risen, perhaps boosted by pharmaceutical marketing and/or because general physicians are more confident prescribing them.[6,12,25]

However, data about the real effectiveness of psychiatric medications are scanty in well controlled clinical trials[5] or even useless.[27] Psychotherapy, other than being a time-consuming and expensive option, has never been proven to exert significant benefits in these patients.[28,29] Even more fancy approaches such as hypnotherapy have no definite value for lack of controlled studies.[30]

In the present study, performed in a large cohort of patients with uninvestigated dyspepsia, the overall frequency of psychiatric drug use, irrespective of the specific compound, was 4.7%. This is a threefold lower value than reported in other series.[25] As previously reported, women treated with these medications largely outnumbered men.[31,32] As expected, psychiatric drugs use was recorded among women since the age of 40, that is, much earlier than among their male peers,[32] probably due to the strong psychosomatic component.[33] Accordingly, in our study, the most used compounds were tranquillizer medications, and among psychiatric drugs SSRIs followed by TCAs. This finding seems to reflect a shift in decision-making of physician as a result of the availability of newer molecules in the market, as well as increased patients' awareness of their benefits.[32]

Polypharmacy (use of agents other than psychiatric and antianxiety drugs) was the strongest predictor of the use of psychiatric drugs usage. Assuming that medications are a proxy of illness, we can suppose that the number of treatments equals number of comorbidities, it is likely that a more sick patient will be more prone to have functional disorders.

Additional factors strongly associated with the usage of psychiatric drugs were marital status and smoking habits. More specifically, married or widowed patients showed a slightly increased risk compared to unmarried ones, probably owing to the fact that the former live in a household context implying a relative stress burden from which unmarried people are often exempted.[34] In contrast, the apparent advantage of unmarried subjects was not shared by divorced subjects. We can speculate that divorce entails a psychological distress followed by psychiatric disturbances such as mood imbalance, sleeping disorders, anxiety, and generalized somatization.[35] Also, widowhood displayed an increased risk, although in this case the confounding effect of advancing age on psychological functions is the most likely explanation.[35] Interestingly, in

our analysis the association of marital status and psychiatric drugs assumption remained significant after adjustment for all covariates, indicating that its effect size is quite robust and should be taken into consideration for the overall clinical management of these patients.

In our study, the status of current or former smoker increased by 32% the risk to take psychiatric drugs and remained significant even in multivariate analysis, but the observational design of the study unfortunately precludes the ascertainment of a potential cause–effect relationship. It may be conjectured that heavy smoking is per se a consequence of anxiety and/or depression able to amplify functional disturbances.[36] Finally, in our study, a protective effect of living in rural areas for taking psychiatric drugs was observed, as previously reported.[34] However, this effect was weak, likely because a real distinction between rural and urban areas is not feasible in Northern Sardinia, where the biggest town does not exceed 130,000 inhabitants. According to observations from Nana et al,[37] the lowest socioeconomic standing was associated with higher frequency of psychiatric drugs use. Similarly to the usage of psychotropic medications, tranquillizer use among the study population followed the same pattern.

In conclusion, the present study confirmed the usage of psychiatric drugs and antianxiety medications in patients with uninvestigated dyspepsia. The amount of medications assumed was positively related to variables previously observed in a number of studies such as female gender, marital status, polypharmacy, smoking habits, and place of residence. More interestingly, the analysis confirmed the existence of a birth cohort effect associated with psychotropic treatments among elderly born after 1950 compared to elderly patients born before 1950, more prominent for antianxiety drugs.

However, this study did not evaluate the first prescription to the patients. In addition, information about the specific reason for drug prescriptions is missing. It is reasonable to consider that in some patients, psychiatric drugs could have been prescribed before the occurrence of dyspeptic symptoms for different reasons such as treatment of pain, sleep, and or mood disorders, and others. Data regarding the severity of psychiatric or anxiety disorders are also lacking in our study. Moreover, the "beneficial influence" of psychiatric treatments on dyspeptic symptoms was not addressed in the cohort of patients studied.

Despite these drawbacks, the results of this study underline that a sizable proportion of Sardinian patients with uninvestigated dyspepsia are prescribed with common psychotropic drugs. More evidence-based guidelines, supported by clinical trials on the effect and long-term outcome of treatment with psychiatric and antianxiety medications in dyspeptic patients are needed.

Acknowledgments

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