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Associations between Medication Use and Functional Gastrointestinal Disorders: A Population-Based Study

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Abstract

Background—Functional GI syndromes are known to be very prevalent but this may be associated with unrecognized medications use. We aimed to estimate the prevalence of PPI, antidepressant, and narcotic use in the general population, and evaluate the association between each medication and functional GI syndromes adjusting for potential confounders.

Methods—In 2008 and 2009, newly revised versions of a validated bowel disease questionnaire were mailed to a community based cohort (total mailed=8006) of Olmsted County, MN residents; 3831 returned the questionnaire (response rate=48.0%). Medication usage, specifically PPIs, narcotics, and antidepressants in the last year, was elicited via three separate questions on the questionnaire. The association between each medication and GI symptom complexes was assessed using multiple variable logistic regression models.

Results—A total of 3515 of the respondents (92%) had complete data (mean age: 61±15; 54% female). The overall proportion reporting PPI use was 20% (95% CI: 19, 22), narcotic use 12% (95% CI: 11, 13), and antidepressant use 15% (95% CI: 14, 16). PPI use was significantly associated with IBS status (OR=1.4, 95% CI 1.1, 1.7) as well as with GERD (OR=3.5, 95% CI 2.7, 4.4) and dyspepsia (OR=2.0, 95% CI 1.5, 2.7). The association of PPI use with IBS was not explained by coexistent GERD or dyspepsia. Antidepressant use was significantly associated only with bloating (OR=1.6, 1.1, 2.2).

Conclusions—Some medications that may alter intestinal transit or bowel flora are commonly utilized by the general population, and PPI use appears to be linked to IBS.

Keywords

Functional GI disorders; proton pump inhibitors; antidepressants; narcotics

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Introduction

Functional gastrointestinal disorders (FGIDs) including dyspepsia, bloating, and irritable bowel syndrome (IBS) are commonly experienced, affecting 10-25% of individuals in the general population (1, 2). Multiple pathophysiologic mechanisms have been explored, but the underlying causal pathways associated with FGIDs remain obscure (3-6).

In the clinic, patients seen by gastroenterologists often have already been prescribed proton pump inhibitors (PPIs), antidepressants, and narcotic pain medicines. According to the national database of retail pharmacy sales, all three medications are among the most commonly prescribed class of medications in the United States (7, 8), and PPIs are the most commonly prescribed drug class for digestive diseases (8).

While functional GI syndromes are known to be very prevalent (5, 9), this may be in part explained by medication use. For example, PPIs have been considered relatively safe, but studies have demonstrated that PPI use is associated with excess bacterial infections and small bowel bacterial overgrowth (10-12). It has been postulated that PPI use through elevated gastric pH levels may facilitate the growth of potentially pathogenic upper gastrointestinal tract organisms, and promote the development of IBS through excess gas production in the small intestine (13, 14). Narcotics have been a mainstay of treatment of nonmalignant chronic pain, but their use has been limited by the induction of bowel dysfunction as well as addiction (15-17). It is conceivable that slowing of intestinal transit by narcotics may lead to small bowel bacterial overgrowth and in turn result in IBS. Moreover, narcotics may also increase nausea that may confuse the diagnosis of dyspepsia. Similarly, antidepressants can have major GI side effects, with tricyclics potentially slowing intestinal transit through cholinergic antagonism, and selective serotonin reuptake inhibitors (SSRIs) accelerating intestinal transit via excess gut serotonin levels (18-20). However, little data are available on the prevalence of medication usage and their association with chronic unexplained GI symptoms in the general population.

Thus, we aimed to estimate the prevalence of use of PPIs, antidepressants, and narcotics in the general population, and evaluate the association between each medication class and functional GI disorders adjusting for potential confounders.

Methods

This study is a population-based cohort study of subjects sent a GI symptom survey in 2008 and 2009 that included medication usage-related questions. This study was approved by the Institutional Review Boards of the Mayo Foundation and the Olmsted Medical Center.

Subjects

In Olmsted County, Minnesota, about 120,000 persons reside (of whom 89% are white). The population has been repeatedly studied because it is representative of U.S. whites across a number of sociodemographic variables (21-25). Mayo Clinic and Olmsted Medical Center are the major providers of medical care to residents in the County and over any 4 year time span almost all residents of the County see one of these providers (26, 27). The Rochester Epidemiology Project therefore links virtually all providers in the County and provides a unique records linkage system so that accurate enumeration of the population is possible and random, representative samples can be drawn (26). These resources have been utilized to investigate the epidemiology of functional GI disorders in this part of the United States in a number of landmark studies (21-25).

Following approval by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center, we used this system previously to draw a series of random samples of Olmsted County residents stratified by age (5-year intervals between 20 and 94 years) and gender (equal numbers of men and women), and to draw a new random sample of Olmsted County residents stratified by age (25-65 years) and gender.

Survey Methods

For the current study, a previously assembled cohort (n=4451) (21-25) and a new age- and gender-stratified random sample (n=3555) (28) of Olmsted County, MN, residents (total mailed=8006) were mailed validated self-report gastrointestinal symptom questionnaires (Talley Bowel Disease Questionnaire [BDQ]) in 2008 and 2009.

The original Talley BDQ (23) was designed to measure the GI symptoms experienced over the previous year, collect past medical history data and assess non-GI somatic symptoms, and it has been modified over time. The original Talley BDQ and modified versions have been shown to be a reliable and valid measure of GI symptoms (29-31). Furthermore, the current modified version of Talley BDQ has also been shown to be reliable and a valid measurement of bowel symptoms (28). The current Talley BDQ consists of 27 gastrointestinal symptoms, the Somatic Symptom Checklist (SSC), and 3 questions about medications use (PPIs, antidepressants, and narcotic pain medication). The SSC consists of questions about relevant symptoms and illnesses (e.g. headaches, backaches, lethargy, insomnia), but excludes any gastrointestinal items, and subjects are instructed to indicate how often each occurred (0=not a problem to 4=occurs daily) and how bothersome each was (0=not a problem to 4=extremely bothersome when occurs) during the past year, using separate 5-point scales (32-34). The overall SSC score is calculated by averaging over the individual frequency SSC item responses, separately the individual bothersome responses and then computing the mean of these two intermediate values. This score has been shown to be a reliable and valid measure of somatization (34, 35).

The study questionnaire and an explanatory letter were mailed to a total of 8006 residents of Olmsted County. Reminder letters were mailed at week 3 to 6 after the initial mailing to nonresponders. Subjects who indicated at any point that they did not wish to complete the survey were not contacted further. Otherwise, nonresponders were contacted by telephone at week 9 to request their participation and verify their residence within the County. A completed questionnaire was returned by 3831 subjects, giving a response rate of 48%. Responders have been shown to be highly representative of the County and response bias appears to be minimal (36).

The questionnaires included questions related to specific medication use (including relevant trade names), and the response options were no or yes for each medication group listed (PPI, narcotics, antidepressants).

The gastrointestinal symptom complexes were defined by specific symptom criteria, each of which was elicited using a 5-category Likert Scale response: “not at all”, “sometimes”, “often”, “most of the time”, “always”:

- **Gastroesophageal reflux (GERD).** GERD was defined as heartburn once a week or more, or acid regurgitation once a week or more.
- **Dyspepsia.** Dyspepsia was defined using Rome III symptom criteria (37), requiring one or more of the following; 1) unable to finish a regular size meal more than once a week, 2) feeling uncomfortably full after a regular size meal more than once a week, 3) pain or burning in the epigastrium more than once a week.

- **Irritable bowel syndrome (IBS).** IBS was defined by Rome III criteria (37) namely, pain or discomfort at least 2 or 3 days per month and 2 or more of the following: 1) pain relieved by bowel movements (BMs), 2) change in frequency (more or fewer), 3) change in consistency (looser or harder).
- **Bloating.** Bloating was defined by feeling bloated or having visible swelling one day a week or more.

Statistical Analyses

The ‘univariate’ associations of reported specific GI symptom complexes with demographic (e.g. age, gender) and clinical characteristics (SSC score, physician visits, and GI conditions) were assessed using logistic regression models, adjusting for age, gender, and SSC score. In addition, two multiple variable logistic regression models were examined separately for each of the GI symptom complexes (e.g., IBS) to estimate the odds for reporting symptoms consistent with the GI symptom complex in those taking a specific medication (i.e., PPI, narcotics, and anti-depressants) relative to those not reporting taking the medication. The first only included age, gender, SSC score and all the medications. The second set of models also included the status for the other GI symptom complexes (i.e., in estimating the odds for IBS, the status of GERD, dyspepsia, and bloating were also included as covariates in the model along with age gender and SSC score and the medications). All analyses were done with SAS version 9.1 (SAS Institute, Cary, NC). A significance level of 0.05 was used, and all tests were two-sided.

Results

Of 3831 responders, a total of 3515 of the respondents (92%) had complete data for this analysis (mean age: 61±15; 54% female). Table 1 summarizes the sociodemographic characteristics, prevalence of medication use, and prevalence of functional gastrointestinal disorders according to functional GI disorder status. The overall proportion reporting PPI use was 20% (95% CI: 19, 22), while narcotic use was 12% (95% CI: 11, 13), and antidepressants use was 15% (95% CI: 14, 16) in the community.

The prevalence of GERD was 12% (95% CI: 11, 13), dyspepsia 10% (95% CI: 9, 11), IBS 19% (95% CI: 18, 21), and bloating 8% (95% CI: 7, 9) in the community. Subjects with GI symptom complexes were younger, more likely to be female, have higher SSC scores, and report more physician visits relative to the total study population. Moreover, the proportions reporting medication usage in subjects with GI symptom complexes were typically higher than the total study population (Table 1). Furthermore, subjects with GI symptom complexes more commonly reported experiencing other GI symptoms relative to subjects without GI symptom complexes or the total population (Table 1).

Medication use and gastrointestinal symptom complexes

Table 2 summarizes the odds ratio (OR) for each gastrointestinal symptom complex in those with specific types of medication use (PPI, narcotics, and antidepressants) relative to those without use, after adjusting for age, gender, and SSC score and the other types of medications used. Overall, age, gender, and SSC score were associated with each GI symptom complex, the odds for each increasing with decreasing age, female gender, and increasing SSC score.

With respect to medication use, PPI use was positively associated with GERD, dyspepsia, IBS, and bloating, adjusting for age, gender, SSC score, and the other two medication types. Use of narcotics was not significantly associated with any of the gastrointestinal complexes.

Use of antidepressants was positively associated only with bloating adjusting for age, gender, SSC score, and the other two medication types (Table 2).

Medication use and GI symptom complexes after adjusting for other GI symptoms

Figures 1 and 2 show odds ratios for each GI symptom complex after adjusting for age, gender, SSC score, specific medications used, and other GI symptom complexes. In the multiple variable model for GERD, decreasing age, increasing SSC score (per unit), dyspepsia, IBS, and bloating were all significantly associated with increased odds for reporting GERD relative to the reference levels for the symptom predictors (Figure 1). As might be expected, PPI use was also significantly associated with GERD status after adjusting all other variables.

In the multiple variable model for dyspepsia, decreasing age, female gender, increasing SSC score (per unit), GERD, IBS, and bloating were significantly associated with increased odds for reporting dyspepsia relative to the reference levels for the symptom predictors (Figure 1). Among the medication types, only PPI use was significantly associated with dyspepsia status after adjusting all other variables.

Decreasing age, female gender, increasing SSC score (per unit), GERD, dyspepsia, and bloating were significantly associated with increased odds for reporting symptoms meeting criteria for IBS (Figure 2). Notably, PPI use was independently associated with IBS status after adjusting for all other variables.

Decreasing age, female sex, increasing SSC score, GERD, dyspepsia, and IBS were all significantly associated with increased odds for reporting bloating (Figure 2). In terms of medication use, only antidepressant use was significantly associated with bloating status after adjusting for all other variables. No associations with narcotic use were identified.

Discussion

In this study, the overall proportion reporting PPI use in a community was estimated to be 20% (95% CI: 19, 22), consistent with national US data (38). The rate of reporting narcotic prescriptions was 12% (95% CI: 11, 13), and of reporting antidepressants use 15% (95% CI: 14, 16), and these are also consistent with US national data (39-41). We observed that the prevalence of GERD was 12%, dyspepsia 10%, IBS 19%, and bloating 8% in this representative community sample, which is very similar to prior studies in Olmsted County and elsewhere (30, 34, 42-44). As might be expected, we found that younger age, female gender, higher somatic symptom score, and greater physician visits were significantly positively associated with each GI symptom complex relative to subjects free of these GI symptom complexes. Notably, we found that PPI use was independently associated with IBS even adjusting for GERD and dyspepsia, while antidepressant use was significantly associated with bloating after adjusting for all other potential confounders. However we did not find any association between GI symptom complexes and narcotic use. To our knowledge, this is the first population-based study to assess the relationship between these medications and chronic unexplained GI symptom complexes in a community; however it cannot be assumed these are necessarily causal relationships based on the study design.

The advent of proton-pump inhibitors for the treatment of acid related GI disease was a revolution in the field. Based on a national database study (8), five proton pump inhibitors dominate the prescription market, comprising 51% of the total number of prescriptions for all the prescription drugs from retail pharmacies for digestive diseases (45). Friedenberg et al. (46) showed that the frequency of ambulatory visits in the United States for GERD and PPI use have both increased significantly between 1995 and 2006, presumably driven in part

by marketing forces. However, there are no solid data on how many people are on PPIs in the general population because it is hard to estimate the prevalence of over the counter drugs use. Our study showed about 20% of a general representative population had taken a PPI in the last year, reflecting a major cost burden on the health care system.

Proton pump inhibitors are considered remarkably safe drugs but recently several concerns have been reported, including osteopenia or osteoporosis with bone fracture (12, 47), community acquired pneumonia (48, 49), *Clostridium difficile* infection (10, 50), and possibly small bowel bacterial overgrowth (13, 51). In the current study, we also found that PPI use was independently associated with GERD and dyspepsia as well as with IBS. The association between PPI use and GERD or dyspepsia might be expected as they are used for the treatment of these problems, but the association with IBS is more concerning. IBS, GERD, and dyspepsia can coexist but the association is greater than expected by chance (9, 42) but we adjusted for such confounding.

One possible explanation for the association between PPI use and IBS in the community is that PPI use could predispose to bacterial overgrowth secondary to reduced gastric acidity, and induce IBS (14). Recently, Lombardo et al. (52) studied the relationship between PPI therapy, IBS, and small intestinal bacterial overgrowth (SIBO) with hydrogen breath testing. They showed that SIBO based on a positive glucose hydrogen breath test (GHBT) was detected in 50% of patients taking PPIs, in 25% of patients with IBS, and in 6% of healthy control subjects. In addition, they showed that the prevalence of SIBO increased after 1 year of treatment with PPI. Thus, PPI therapy might predispose to SIBO. Spiegel et al. (14) have proposed the 'PPI-IBS confounding hypothesis', which specified that the apparent relationship between IBS and SIBO could potentially be confounded by the use of PPIs, with IBS patients taking more the PPIs than controls (perhaps related to the known overlap of IBS with GERD). PPI therapy in turn may promote SIBO by eliminating gastric acid; in previous studies of SIBO and IBS, PPI therapy was not controlled for in the analyses (53-55). Our analyses controlled for the overlap of IBS with GERD or dyspepsia, and PPI use remained associated with IBS. Thus our data do *not* support the Spiegel 'PPI-IBS confounding hypothesis' but rather suggest a direct link (although the data do not establish beyond doubt that such a link is causal because of the cross-sectional design, which may have led to confounding by indication or reverse causality as discussed below).

Opioids are used extensively for treating moderate to severe pain secondary to malignancy, but narcotic prescription patterns for nonmalignant pain also appear to be increasing (56). Several studies have shown that the prevalence of regular opioid use (at least several times a week for a month) in the general population ranges from 2.0% to 3.5% (39, 57-59). Our study observed about 12% of the general population took an opioid in the last year. The differences in the prevalence of opioid use among studies might be related to study population, definition of opioid use including duration, or how use was measured. Because opiates slow gastrointestinal motility through the mu-receptor (16, 60-62), opiates induce bowel dysfunction and symptoms such as constipation, nausea, bloating, and sometimes worsening abdominal pain (15-17). Our study evaluated the association of opioid use with lower and upper GI symptom complexes, but we did not find any association. Our study could not assess opioid use details (e.g. dose or duration of opioid use) and many may have only been taking short term opioids.

Antidepressants have recently become one of the most commonly prescribed classes of medications in the United States (40, 41, 63, 64). According to several studies (63-66), prescribing of antidepressants has dramatically increased over time, with up to 10% of the population taking this drug class in 2005 (65). Our study also showed that the overall prevalence of antidepressant use in the population was 15%. While antidepressants are used

to treat functional GI symptoms, they can also have GI side effects, so we evaluated the association between antidepressant use and GI symptom complexes. Interestingly, we found that antidepressant use was only associated with bloating, not with dyspepsia or IBS. The possible explanation for the association of antidepressants with bloating may be that some antidepressants slow GI motility and delay gastric emptying (20, 67), which might eventually evoke bloating symptoms. It is also possible antidepressants promote small bowel bacterial overgrowth, particularly tricyclics. Alternatively, more people with bloating may be prescribed this drug class although no firm data exist to support this indication.

The strengths of the current study include the investigation of a random community sample. We avoided just studying health care seeking subjects which should have minimized or avoided selection bias, and this sample provided an excellent opportunity to study the relationship between medication use and gastrointestinal symptom complexes. A carefully validated questionnaire was also applied.

Limitations of our work include the lack of detail about actual medication use (e.g., dose, chronicity, or frequency of the medication). We only have dichotomous medication data (yes and no). For example, we could not distinguish tricyclic from selective serotonin reuptake inhibitor antidepressant effects in the analyses. Also, we cannot conclude there is a definite causal association between symptom-based GI disorders and medication use because of the inherent difficulties in a cross sectional study design; there might be an increased use of the drug to treat the disorder, or the drug itself might induce the symptoms on which the diagnosis is based. A possible additional limitation was a lack of clinical detail regarding structural disease, although in most cases we would expect investigations to be negative or normal. Despite these limitations, this study presents important descriptive information on the epidemiology of medication use and chronic GI symptoms in a community. In addition, our data may not be generalized to the whole U.S. population because the racial composition of this community is predominantly white. However, while the prevalence of GI symptom complexes and medication use may vary by ethnic group, at a minimum our data are generalizable to U.S. Caucasians.

We conclude from this population-based study that proton pump inhibitors, antidepressants, and narcotics are commonly utilized by the general population. IBS in particular was associated with PPI use despite considering confounding, but it is unknown if this reflects a true cause and effect relationship.

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Odds Ratio (95% CI) for GERD

Odds Ratio (95% CI) for Dyspepsia

Figure 1. Odds Ratios for a. GERD and b. dyspepsia, adjusted for all variables listed

Odds Ratio (95% CI) for Irritable Bowel Syndrome

Odds Ratio (95% CI) for Bloating

Figure 2.
Odds Ratios for a. IBS and b. bloating, adjusted for all variables listed.

Table 1

Sociodemographic characteristics of the study cohort

	Total N=3515	GERD n=408 (11.6%)	Dyspepsia n=344 (9.8%)	IBS n=683 (19.4%)	Bloating n=296 (8.4%)
Age, mean $\pm$ SD	61 $\pm$ 15	59 $\pm$ 16	59 $\pm$ 16	57 $\pm$ 16	57 $\pm$ 15
Female gender	1908 (54%)	254 (62%)	243 (71%)	471 (69%)	221 (75%)
Mean SSC score	0.8 $\pm$ 0.6	1.2 $\pm$ 0.8	1.4 $\pm$ 0.8	1.2 $\pm$ 0.7	1.3 $\pm$ 0.8
Visiting physician >5 times	368 (10%)	79 (19%)	77 (22%)	118 (17%)	62 (21%)
Medication					
PPIs	713 (20%)	193 (47%)	150 (44%)	210 (31%)	103 (35%)
Narcotics	412 (12%)	77 (19%)	73 (21%)	122 (18%)	55 (19%)
Antidepressants	514 (15%)	89 (22%)	98 (28%)	159 (23%)	92 (31%)
Other GI symptom complex					
GERD	408 (12%)		144 (42%)	163 (24%)	109 (37%)
Dyspepsia	344 (10%)	144 (35%)		182 (27%)	148 (50%)
IBS	683 (19%)	163 (40%)	182 (53%)		176 (59%)
Bloating	296 (8%)	109 (27%)	148 (43%)	176 (26%)	

IBS = irritable bowel syndrome

SSC =somatic symptom checklist

PPI = proton pump inhibitors

GERD = gastroesophageal reflux disease

Table 2
Multiple variable model estimated Odds Ratios[†] for each GI symptom complex in those with medication use relative to those without medication use

	GERD	Dyspepsia	IBS	Bloating
Age, per 10 years	0.8 (0.8,0.9)	0.9 (0.8,1.0)	0.8 (0.8,0.9)	0.8 (0.7,0.9)
Female gender	1.1 (0.9,1.4)	1.7 (1.3,2.2)	1.8 (1.5,2.2)	2.0 (1.5,2.7)
SSC score, per unit	2.4 (2.0,2.8)	3.1 (2.6,3.7)	2.9 (2.5,3.4)	2.9 (2.4,3.5)
Medication				
PPIs	3.9 (3.1,5.0)	2.7 (2.1,3.4)	1.6 (1.3,2.0)	1.6 (1.2,2.1)
Narcotics	1.1 (0.8,1.5)	1.2 (0.8,1.6)	1.1 (0.9,1.4)	0.9 (0.6,1.3)
Antidepressants	0.9 (0.7,1.2)	1.3 (1.0,1.8)	1.1 (0.9,1.4)	1.6 (1.2,2.1)

[†]Odds Ratios adjusted for other predictor variables listed in left most column.

IBS = irritable bowel syndrome

SSC = somatic symptom checklist

PPI = proton pump inhibitors

GERD = gastroesophageal reflux disease