PREVALENCE AND DETERMINANTS OF GASTROINTESTINAL SYMPTOMS IN THE DUTCH COMMUNITY

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General Introduction
Gastrointestinal symptoms stem from organs that constitute the gastrointestinal tract, from the mouth to the rectum. These symptoms have a broad spectrum, and include nausea, abdominal fullness, vomiting, regurgitation, diarrhoea, constipation and bloody stools. Symptoms originating from the upper gastrointestinal tract can be described as ‘dyspepsia’. This word has been derived from the Greek words “día” (dus = bad) and “πεπτίω” (peptien = to digest), and refers to problems with digestion of food and chronic or recurrent discomfort or pain in the upper abdomen. Patients can present with any combination of upper gastrointestinal symptoms, making the variation in clinical presentation of patients with dyspepsia very broad.

Causes of dyspepsia can be classified into two main categories: “organic” and “functional”. Gastroesophageal reflux disease (GERD) and peptic ulcer disease are the most common organic causes and are present in 25-40% of patients with dyspeptic symptoms in primary care. The prevalence of gastric or oesophageal cancer in patients with dyspepsia without alarm symptoms is less than 1%. Dyspepsia is called “functional”, in case diagnostic workup does not yield any abnormalities.

The prevalence of dyspepsia in western countries varies between 10% and 40% (Figure 1). Reasons for the large range in reported prevalence include variations in: time period, definition used, country of origin and method of data collection.
During the last 20 years, prevalence of risk factors for gastrointestinal symptoms has changed dramatically. New causes of gastrointestinal symptoms, e.g. widespread non-steroidal anti-inflammatory drug (NSAID) and aspirin use, have emerged, while other factors, as the prevalence of Helicobacter pylori, have significantly declined.\textsuperscript{23-24} Due to these changes an update of the current population prevalence is warranted. The importance for a critical reconsideration regarding the current prevalence is emphasised by the large burden on our healthcare system, healthcare budget and individual health-related quality of life.\textsuperscript{25-27} This is caused by the high prevalence and by the chronic, recurring symptom pattern of many gastrointestinal symptoms.

**PATHOGENESIS**

Functional dyspepsia is assumed to be a multifactorial disease, resulting from the interaction of biological, psychological and social factors.\textsuperscript{29} Studies in patients with functional dyspepsia have found that impaired gastric accommodation is present in approximately 40% of patients.\textsuperscript{29,30} It is hypothesised that due to impaired relaxation, the gastric wall tension increases, which is associated with dyspeptic symptoms.\textsuperscript{31} Delayed gastric emptying is also a mechanism that has been associated with functional dyspepsia. In a meta-analysis, delayed gastric emptying was found in more than 35% of patients with dyspepsia.\textsuperscript{32} On the other hand there are also indications that rapid and not delayed gastric emptying causes dyspeptic symptoms.\textsuperscript{33} It is thought that visceral hypersensitivity also plays a role in patients with functional dyspepsia. Visceral hypersensitivity is defined as an increased perception to visceral stimuli. Several studies have demonstrated an abnormal visceral sensory function in patients with functional dyspepsia.\textsuperscript{34-37} Anxiety disorders, depression and somatoform disorders are more frequently diagnosed in patients with functional dyspepsia and the association between psychosocial factors and presence of gastrointestinal symptoms has been reported in multiple studies.\textsuperscript{38-40} This association is present in the dyspepsia population that visits secondary and tertiary care centers, but also among the general population.\textsuperscript{38,41,42}

*Helicobacter pylori* infection is a cause of organic dyspepsia. Since the initial discovery of *H. pylori* in 1982 by Robin Warren and Barry Marshall, the prevalence of *H. pylori* has decreased from 38% to 11% of the general Dutch population.\textsuperscript{2,43} A higher prevalence is found in older patients and in patients from non-western countries.\textsuperscript{23-43} Simultaneous with the decreasing prevalence of *H. pylori* infection, the prevalence of reflux disease in the western world has increased.\textsuperscript{44} Gastroesophageal reflux disease (GERD) is defined by frequent symptoms of heartburn and/or regurgitation, which arise when reflux of stomach contents causes symptoms. The prevalence of GERD in Western countries is 10%-20%.\textsuperscript{16,45} GERD symptoms are included in some definitions of dyspepsia, while other classifications consider these symptoms as a separate entity.

**CLINICAL EVALUATION**

The Dutch guideline “dyspepsia” is recently updated and recommends the following assessment of upper gastrointestinal symptoms (Figure 2).\textsuperscript{46}

![Figure 2: Clinical evaluation according to the Dutch guideline](image)

If a patient presents with upper gastrointestinal symptoms without alarm symptoms, use of gastrotoxic medication has to be evaluated. If this medication is not used, empirical treatment with acid suppressants can be initiated. The Dutch guideline recommends a step-up approach preserving the potent proton pump inhibitors (PPIs) for patients with persistent upper gastrointestinal symptoms, despite antacids and/or *H. pylori* test and treat strategy can be initiated for patients originating from countries with a high *H. pylori* prevalence, or in patients with persistent or recurrent upper gastrointestinal symptoms.\textsuperscript{47-50} If alarm symptoms are present, such as unintentional...
weight loss and/or dysphagia, an upper endoscopy should be performed directly. Routine laboratory testing is not recommended. Additional investigations are being performed in less than 25% of patients who present with upper gastrointestinal symptoms in primary care.\textsuperscript{51-53} In primary care studies, 60%-70% of patients with upper gastrointestinal symptoms who undergo endoscopy, no or irrelevant abnormalities will be found.\textsuperscript{1,2}

In the international medical literature, Rome criteria are used to categorise functional gastrointestinal disorders.\textsuperscript{54} The definition of functional dyspepsia according to the most recent Rome III criteria consists of at least one of the following symptoms: bothersome postprandial fullness, early satiety, epigastric pain or epigastric burning without evidence of structural disease (including upper endoscopy) that is likely to explain the symptoms. These symptoms must be present for the last 3 months; and the onset was at least 6 months prior to diagnosis.\textsuperscript{55}

THERAPEUTIC OPTIONS

If functional dyspepsia is suspected, treatment with an antacid or H\textsubscript{2}RA may be initiated according to the Dutch guideline. However, the current daily practice is that a PPI is the most frequently prescribed medication in patients with upper gastrointestinal symptoms (data from the Dutch Foundation for Pharmaceutical Statistics, SFK). The beneficial effects of PPIs have been widely proven in the treatment of GERD.\textsuperscript{56-59} In dyspepsia, the PPI efficacy is less obvious. A meta-analysis that compared PPIs with placebo in patients with functional dyspepsia found that PPIs were more effective with an estimated number needed to treat of 15 (95\% CI, 8.7 - 57.1).\textsuperscript{60} H\textsubscript{2}RAs are also superior to placebo in the treatment of functional dyspepsia, but the evidence is weaker.\textsuperscript{61}

Prokinetics, as domperidon, are also used in the treatment of dyspepsia. This is based on the hypothesis that decreased motility is one of the contributing factors in dyspepsia. Most studies that assessed prokinetic drugs in functional dyspepsia have been performed with cisapride and which demonstrated that cisapride was more effective than placebo.\textsuperscript{62} However, these studies have limited methodological quality and cisapride was withdrawn from the Dutch market in 2009 due to cardiovascular side effects (i.e. QT prolongation).\textsuperscript{63}

In patients with functional dyspepsia not responding to the previously described treatment options, treatment with antidepressants can be considered.\textsuperscript{64-66}
RESEARCH QUESTIONS IN THIS THESIS

1 What is the current prevalence of gastrointestinal symptoms in the Dutch general population?
   1a What is the current prevalence of gastrointestinal symptoms in general in the general population? (Chapter 2)
   1b What is the prevalence of GERD symptoms in a sample of Dutch internet users? (Chapter 3)
   1c What is the behaviour of GERD over time, assessed in an Internet population? (Chapter 4)
   1d What is the gastrointestinal symptom presence in users of plain low-dose aspirin compared to users of buffered aspirin in the general population? (Chapter 6)
   1e What is the association between antidepressant use and presence of gastrointestinal symptoms in the general population? (Chapter 9)

2 What is the consequence of gastrointestinal symptom presence on health-related quality of life?
   2a What is the health-related quality of life in respondents with gastrointestinal symptoms in the general adult population? (Chapter 2)
   2b What is the health-related quality of life in respondents with GERD in an internet population? (Chapter 3)

3 What is the role of NSAIDs on gastrointestinal symptoms and complications?
   3a What risk factors for gastrointestinal complications are present in international guidelines for NSAID users? (Chapter 5)
   3b Is there a difference in prevalence of gastrointestinal symptoms between users of prescribed NSAIDs and over-the-counter (OTC) NSAIDs? (Chapter 6)

4 What is the role of PPIs in the treatment of gastrointestinal symptoms?
   4a What is the effectiveness of PPIs in respondents with GERD, followed via the Internet? (Chapter 4)
   4b What is the PPI-coprescription rate in NSAID users at increased risk for gastrointestinal complications? (Chapter 6)
   4c Can PPIs relieve NSAID-associated upper gastrointestinal symptoms? (Chapter 7)

In order to address the abovementioned issues we used 3 different study models.

1. QUESTIONNAIRES
We have chosen to study the general population because gastrointestinal symptoms are frequently present and only a subset of persons with gastrointestinal symptoms will end up in the healthcare system (see Figure 4).

Figure 4: Studied populations in this thesis

We developed a questionnaire to assess presence of symptoms derived from the whole gastrointestinal tract. Most questionnaires are focussed on presence of a specific disease, like dyspepsia, GERD, irritable bowel syndrome (IBS) etc, while our aim was to assess the entire gastrointestinal system.

Our questionnaire was used previously and has been adapted over time. The questionnaire has not yet been validated. However, a first step was made, during a study in which the answers of the gastrointestinal symptom assessment on the questionnaire were compared with answers obtained via an interview. This study concluded that the 7-point Likert scale for symptom assessment was comprehensible and had a good reproducibility for measuring the presence of gastrointestinal symptoms. As main drawback, the symptom severity was consistently rated higher in the questionnaire compared to the interview. The questionnaire was subsequently slightly adapted and tested in a pilot study involving more than 1500 subjects.

To assess health-related quality of life, we added the widely used general health-related quality of life questionnaire “EuroQol EQ-5D” to the questionnaire used in our large general population survey. We submitted the questionnaire to 5 different communities in the Netherlands (Almere: 10,000 questionnaires; Den Haag: 10,000; Nijmegen: 20,000; Heumen: 6,012;...
Wijchen: 5,857. We chose these communities to obtain a representative geographical distribution; east versus west, village versus city. The advantage of using a paper-based questionnaire is that respondents can complete the questionnaire at a moment they prefer. As this is a frequently used method, the vast majority of participants know how to complete such a questionnaire. The disadvantage is that respondents can skip questions or that answers are unreadable, leading to incomplete questionnaires. These disadvantages are not present with internet based surveys. The drawback of surveys via the internet is selection bias, which will be higher compared to paperbased questionnaires, and the inability of a subset of the general population to use the internet properly.  

To acquire a complete and complementary overview of the general population, we employed both methods (a web and paperbased questionnaire). By using both methods we are able to assess baseline characteristics, medication use, a broad spectrum of gastrointestinal symptoms, and health-related quality of life.

2. SYSTEMATIC REVIEW
To assess risk factors for gastrointestinal complications in NSAID users, we performed a systematic review of guidelines and consensus agreements that have been published in the international literature. As mentioned above, NSAID use is associated with gastrointestinal complications. The risk for patients to develop these complications is dependent on the presence of risk factors. Advanced age, co-medication and history of peptic ulcer disease are established risk factors. Although multiple studies have demonstrated a large number of risk factors, we still lack in depth quantitative knowledge how to interpret these data for the individual patient. For example, age is a well-known risk factor but we do not know at which age we should start to advice a gastroprotective strategy. Ideally we should be able to identify only those patients that have an increased risk for gastrointestinal complications and actively offer them a gastroprotective strategy. Several guidelines were published to help to identify ‘at risk’ patients. We will study the level of agreement in these guidelines.

3. PROSPECTIVE INTERVENTION STUDY
According to the Dutch guideline, NSAID use is an important cause of upper gastrointestinal symptoms and should always be questioned during history taking. To assess whether PPIs could relieve gastrointestinal symptoms in NSAID users in clinical daily practice, we performed a trial in primary care that included NSAID users who presented with upper gastrointestinal symptoms. Most studies that assessed PPI efficacy in NSAID users, focused on gastrointestinal complications. Only few studies assessed gastrointestinal symptoms as primary outcome. We chose to perform an open-label study in primary care to resemble daily clinical practice as closely as possible. The advantage of our study method was the lower rate of selection bias, because subjects with comorbidity and co-medication were also included. The disadvantage of this study method was that we did not perform endoscopy to exclude other causes of symptoms and the study was not blinded and placebo controlled.

OUTLINE OF THE THESIS
In Chapter 1, “the General Introduction”, we depicted a framework and provided background for this thesis. In Chapter 2 we will assess the prevalence of gastrointestinal symptoms and its association with health-related quality of life in a sample of randomly selected Dutch inhabitants. In Chapter 3 we will describe the presence of GERD and persistent symptoms in PPI users in website visitors of a dedicated GERD website who completed the GerDQ self-assessment questionnaire. We will highlight patterns of healthcare visits and symptoms over time of this internet population in Chapter 4. Guidelines and consensus agreements regarding gastrointestinal risk factors in NSAID users are systematically reviewed in Chapter 5. Chapter 6 describes the prevalence of gastrointestinal symptoms in OTC and on prescription NSAID users and assesses concomitant PPI use in those NSAID users at increased risk for gastrointestinal complications. The focus of Chapter 7 is the effectiveness of PPIs on NSAID-induced gastrointestinal symptoms in a daily clinical practice setting in primary care. In Chapter 8 we will assess the prevalence of gastrointestinal symptoms in low-dose aspirin users, with a comparison between acetylsalicylic acid and carbamate calcium users. Chapter 9 describes the association between gastrointestinal symptoms and antidepressants use. We complete this thesis by a General Discussion (Chapter 10) that summarizes and discusses the main findings of this thesis.
REFERENCES


Chapter 1


Part 1

Prevalence and impact of gastrointestinal symptoms
Chapter 2

Gastrointestinal symptoms are still prevalent and negatively impact health-related quality of life:

a large cross-sectional population-based study in the Netherlands

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Jeroen Jaspers Focks
Leo GM van Rossum
Ties Eikendal
Jan BMJ Jansen
Robert JF Laheij
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ABSTRACT

Background Over the last decades important risk factors for gastrointestinal symptoms have shifted, which may have changed its population prevalence. The aim of this study was to assess the current prevalence of gastrointestinal symptoms, appraise associated factors and assess health-related quality of life in the general population.

Methods A total of 51,869 questionnaires were sent to a representative sample of the Dutch adult general population in December 2008. Demographic characteristics, gastrointestinal symptoms, health-related quality of life, medication use and comorbidity were reported. We used multivariable logistic regression analysis to determine factors associated with gastrointestinal symptoms.

Results A total of 18,317 questionnaires were returned, and 16,758 were eligible for analysis. Prevalence of gastrointestinal symptoms was 26%. Most frequent symptoms were bloating (63%), borborygmi (60%) and flatulence (71%). Female gender (adjusted OR (aOR) 1.59, 95% CI 1.43 - 1.77), asthma/COPD (aOR 1.47, 95% CI 1.21 - 1.79), use of paracetamol (aOR 1.33, 95% CI 1.20 - 1.47), antidepressants (aOR 1.56, 95% CI 1.22 - 2.00) and acid-suppressive medication were independently associated with presence of gastrointestinal symptoms. Age over 65 years (aOR 0.75, 95% CI 0.65 - 0.87), and use of statins (aOR 0.75, 95% CI 0.61 - 0.93) were associated with a lower prevalence of gastrointestinal symptoms. Respondents with gastrointestinal symptoms had a lower mean health-related quality of life of 0.81 (SD=0.21) compared to 0.92 (SD=0.14) for persons without gastrointestinal symptoms (p < 0.01).

Conclusions Prevalence of gastrointestinal symptoms in the Dutch community is high and associated with decreased health-related quality of life.

INTRODUCTION

Gastrointestinal symptoms are highly prevalent in the general population and are a frequent cause for consultation of a general practitioner.1 Individuals with gastrointestinal symptoms contribute heavily to healthcare utilization and budgeting. The yearly costs for individual patients with gastrointestinal symptoms are steep. For example, in the United States average direct healthcare costs for a number of symptoms such as constipation ($7522), functional abdominal pain ($7646) and irritable bowel syndrome ($5049) are considerable.2 Large population studies in Western countries reported a widely ranging prevalence of dyspepsia from 10% to more than 50%.3,4,5,6 However, these studies were performed about 20 years ago and the risk factor profile for gastrointestinal symptoms has shifted since. For example, the incidence of Helicobacter pylori has rapidly decreased in the industrialized world,7,8 while use of proton pump inhibitors (PPIs) has been on the rise.9-11 Simultaneously, use of gastrotoxic medication, e.g. non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin, is high.12 Finally, there is a global epidemic of obesity, which is associated with gastrointestinal symptoms and disorders, especially gastroesophageal reflux disease (GERD).13,14 The overall prevalence of upper gastrointestinal symptoms ranged from 24% to 45% in a recent study in 13 European countries.15 Although performed in the current era, this study emphasized on socioeconomic factors, and did not report associations between gastrointestinal symptoms and modifiable factors such as BMI and smoking on an individual level.16

Health-related quality of life is an important parameter in modern medicine and refers to the extent that an individual’s physical, emotional and social well-being is affected by a medical condition and its treatment. Individuals with gastrointestinal symptoms report a lower health-related quality of life,17 but this has been mainly studied in a subgroup of patients that have presented to a healthcare provider, which may not be a representative group. The exact impact of gastrointestinal symptoms on all domains of health-related quality of life in the general – including non-healthcare visiting – population remains unclear. Given abovementioned considerations, new data on the prevalence of gastrointestinal symptoms in the general population are warranted. We hypothesize that the prevalence, despite all changes, has remained stable. The aims of our study were to assess: 1) the prevalence of gastrointestinal symptoms in the general population; 2) factors associated with presence of gastrointestinal symptoms; and 3) the effect of gastrointestinal symptom presence on health-related quality of life.
MATERIAL AND METHODS

STUDY POPULATION

We sent 51,869 questionnaires by postal mail to a sample of the Dutch population in December 2008. Invited subjects were at least 18 years and randomly selected from municipal databases of five different municipalities. These villages and cities were selected on their geographical location in The Netherlands, in order to fetch a representative sample. We included returned questionnaires until the end of March 2009. We excluded returned questionnaires with (1) missing of all baseline variables, (2) missing of all gastrointestinal symptoms, (3) missing of the primary outcome measure, or (4) unreadable input about medication use.

The Medical Ethical Committee of the Radboud University Nijmegen assessed the proposal of this study and concluded that it could be waived for ethical review, as questionnaires were returned and stored anonymously, and (non-)responders would not be contacted again. For this reason, we did not obtain written informed consent of all participants.

QUESTIONNAIRE

The questionnaire we used was specifically designed to assess demographic information, gastrointestinal symptoms, medication use, healthcare visits, and health-related quality of life, and has been used before. Respondents were asked whether they suffer from gastrointestinal symptoms in general and subsequently for presence of 26 gastrointestinal symptoms including nausea, early satiety, bloating, constipation and diarrhoea. Severity of gastrointestinal symptoms was assessed on a seven-point scale (0 = absent, 1 = almost absent, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe) during the preceding four weeks. A symptom was considered to be present when scored ≥ 2.

Our primary outcome was the presence or absence of gastrointestinal symptoms, which was assessed with the question: “Do you experience gastrointestinal complaints?” and had to be answered with either “yes” or “no”. Secondary outcomes were type of gastrointestinal symptoms experienced in the preceding four weeks and health-related quality of life, which was assessed with the validated EQ-5D questionnaire. The EQ-5D comprises 5 domains of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has 3 degrees of severity: no problems, some problems or extreme problems. The EQ-5D tariffs were calculated by using Dutch coefficients for Time Trade Off tariffs. The EQ-5D questionnaire also contains a visual analogue scale (EQ VAS), ranging from the worst imaginable health status to the best imaginable health status.

We defined excessive consumption of alcohol as ≥ 14 units (women) or ≥ 21 units (men) per week. Body mass index (BMI in kg/m²) was categorized in < 25 (normal weight) and 25 or more (overweight or obese). Excessive coffee consumption was defined as ≥ 42 cups or more per week.

STATISTICAL ANALYSIS

We analyzed data using Statistical Package for the Social Sciences (SPSS), version 16.0 (IBM Corporation, New York, United States). Frequency tables were provided for respondents’ characteristics and for secondary outcomes. Pearson’s chi-square (χ²) analysis was used to compare categorical variables between respondents with and without presence of gastrointestinal symptoms. Continuous variables were compared between the two groups using Student’s t-test or Mann-Whitney U method whenever appropriate. We calculated presence of various symptoms at various ages by calculating symptom presence per 10 years. Univariable and multivariable logistic regression analysis were performed to identify factors associated with gastrointestinal symptoms. Odds ratios and 95% confidence intervals were stated. Covariates were included in multivariable regression analysis based on a predefined conceptual model that was based on published literature. We also included covariates if they were univariately associated with the primary outcome (p < 0.01).

Health-related quality of life was compared between respondents with and without gastrointestinal symptoms. The 5 domains of the EQ-5D questionnaire were compared using χ² analysis. Dutch utility scores for every individual symptom in persons reporting gastrointestinal symptoms were calculated to assess the impact of an individual symptom on health-related quality of life. Correlation between gastrointestinal symptom score (VAS) and health-related quality of life (EQ VAS) was calculated with a Spearman correlation. A p-value < 0.01 was assumed to be statistically significant.

RESULTS

A total of 18,317 (35%) questionnaires were returned, of which 742 returned unopened and uncompleted. After applying our predetermined exclusion criteria, a total of 16,758 questionnaires were included in our analyses (Figure 1). In total, 4,315 persons (26%) reported gastrointestinal symptoms, with a median symptom duration of 8 years (interquartile range 3-18 years). Compared to participants not reporting symptoms, those with gastrointestinal symptoms were younger (48.9 ± 16 vs. 50.2 ± 16 years), more often female (66% vs. 53%), and reported more frequently use of any medication (overall 80% vs. 67%, Table 1).

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The most frequently reported upper gastrointestinal symptoms were bloating (63%) and belching (45%; Table 2). Flatulence (71%) and borborygmi (60%) were the most frequently reported lower gastrointestinal tract symptoms (Table 3). Distribution of symptom presence among different age categories is depicted in Table 4. The overall prevalence of gastrointestinal symptoms decreased with ageing. This was apparent in females (p<0.01), but not in males (p=0.22; Supplementary Table 1). There was no effect of Body mass index on upper versus lower gastrointestinal symptoms (data not shown).

Table 1: Population characteristics and factors associated with gastrointestinal symptom presence

<table>
<thead>
<tr>
<th></th>
<th>Respondents with gastrointestinal symptoms</th>
<th>Respondents without gastrointestinal symptoms</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±SD)</td>
<td>48.9 (16)</td>
<td>50.2 (16)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>≥ 65 years (%)</td>
<td>747/4,300 (17)</td>
<td>2,451/12,389 (20)</td>
<td>0.85 (0.78 - 0.93)</td>
<td>0.75 (0.65 - 0.87)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>2,784/4,217 (66)</td>
<td>6,448/12,079 (53)</td>
<td>1.70 (1.58 - 1.83)</td>
<td>1.59 (1.43 - 1.77)</td>
</tr>
<tr>
<td>Body mass index ≥ 25 kg/m(^2) (%)</td>
<td>2,067/4,224 (47)</td>
<td>5,549/12,213 (45)</td>
<td>1.15 (1.07 - 1.23)</td>
<td>1.02 (0.92 - 1.13)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>840/4,247 (20)</td>
<td>2,089/12,242 (17)</td>
<td>1.20 (1.10 - 1.31)</td>
<td>1.12 (0.98 - 1.27)</td>
</tr>
<tr>
<td>Excessive alcohol consumption (%)</td>
<td>384/2,919 (14)</td>
<td>1,229/9,266 (13)</td>
<td>1.02 (0.90 - 1.15)</td>
<td>0.93 (0.81 - 1.07)</td>
</tr>
<tr>
<td>Excessive coffee consumption (%)</td>
<td>352/3,612 (10)</td>
<td>1,241/10,828 (12)</td>
<td>0.83 (0.74 - 0.95)</td>
<td>0.87 (0.74 - 1.02)</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>238/4,315 (6)</td>
<td>639/12,443 (5)</td>
<td>1.08 (0.93 - 1.26)</td>
<td>0.85 (0.64 - 1.13)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>316/4,315 (7)</td>
<td>457/12,443 (4)</td>
<td>2.07 (1.79 - 2.40)</td>
<td>1.27 (0.99 - 1.62)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>393/4,315 (9)</td>
<td>651/12,443 (6)</td>
<td>1.82 (1.59 - 2.07)</td>
<td>1.47 (1.21 - 1.79)</td>
</tr>
<tr>
<td>Medication use (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td>1,161/4,315 (27)</td>
<td>610/12,443 (5)</td>
<td>7.14 (6.43 - 7.94)</td>
<td>9.28 (7.91 - 10.9)</td>
</tr>
<tr>
<td>H2RAs</td>
<td>212/4,315 (5)</td>
<td>75/12,443 (1)</td>
<td>8.52 (6.53 - 11.1)</td>
<td>9.90 (6.72 - 14.7)</td>
</tr>
<tr>
<td>Antacids</td>
<td>588/4,315 (14)</td>
<td>437/12,443 (4)</td>
<td>4.33 (3.81 - 4.93)</td>
<td>4.22 (3.53 - 5.05)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>2,529/12,443 (6)</td>
<td>5,763/12,443 (46)</td>
<td>1.64 (1.53 - 1.76)</td>
<td>1.33 (1.20 - 1.47)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1,076/12,443 (25)</td>
<td>2,157/12,443 (17)</td>
<td>1.58 (1.46 - 1.72)</td>
<td>1.02 (0.90 - 1.15)</td>
</tr>
<tr>
<td>Antiplatelet therapy(b)</td>
<td>462/4,315 (11)</td>
<td>1,221/12,443 (10)</td>
<td>1.10 (0.98 - 1.23)</td>
<td>1.06 (0.89 - 1.30)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>278/4,315 (6)</td>
<td>423/12,443 (3)</td>
<td>1.96 (1.68 - 2.29)</td>
<td>1.56 (1.22 - 2.02)</td>
</tr>
<tr>
<td>Statins</td>
<td>435/4,315 (10)</td>
<td>1,285/12,443 (10)</td>
<td>0.97 (0.87 - 1.08)</td>
<td>0.75 (0.61 - 0.93)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>339/4,315 (8)</td>
<td>716/12,443 (6)</td>
<td>1.40 (1.22 - 1.60)</td>
<td>1.22 (0.99 - 1.51)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>487/4,315 (11)</td>
<td>1,286/12,443 (10)</td>
<td>1.10 (0.99 - 1.23)</td>
<td>0.87 (0.71 - 1.06)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>227/4,315 (5)</td>
<td>727/12,443 (6)</td>
<td>0.90 (0.77 - 1.04)</td>
<td>0.81 (0.62 - 1.06)</td>
</tr>
<tr>
<td>Angiotensin-receptor antagonist</td>
<td>186/4,315 (4)</td>
<td>517/12,443 (4)</td>
<td>1.04 (0.88 - 1.23)</td>
<td>0.77 (0.58 - 1.03)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>390/4,315 (9)</td>
<td>1,052/12,443 (9)</td>
<td>1.08 (0.95 - 1.22)</td>
<td>0.85 (0.68 - 1.08)</td>
</tr>
</tbody>
</table>

\(\text{ACE: angiotensin converting enzyme, COPD: chronic obstructive pulmonary disease, H2RAs: histamine H2 receptor antagonists, NSAIDs: nonsteroidal anti-inflammatory drug, PPI: proton pump inhibitor}

\(\text{\(a\)Adjusted for all variables depicted in this table}

\(\text{\(b\)Excessive alcohol consumption is 14 units or more a week for women and 21 units or more a week for men}

\(\text{\(c\)Excessive coffee consumption was defined as 42 cups a week and more}

\(\text{\(d\)Low-dose acetylsalicylic acid, carbassalate calcium, clopistogel and dipryridamol are taken together}

Figure 1: Flowchart
\(\text{* Some respondents fulfilled more than 1 exclusion criterion}
Table 2: Type and frequency of upper gastrointestinal symptoms in respondents experiencing gastrointestinal symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of respondents n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epigastric pain</strong></td>
<td></td>
</tr>
<tr>
<td>In general</td>
<td>1,407/3,842 (36.6)</td>
</tr>
<tr>
<td>During daytime</td>
<td>1,422/3,565 (39.9)</td>
</tr>
<tr>
<td>At night</td>
<td>867/3,452 (25.1)</td>
</tr>
<tr>
<td><strong>Heartburn</strong></td>
<td></td>
</tr>
<tr>
<td>In general</td>
<td>1,366/3,916 (34.9)</td>
</tr>
<tr>
<td>During daytime</td>
<td>1,250/3,537 (35.3)</td>
</tr>
<tr>
<td>At night</td>
<td>953/3,494 (27.3)</td>
</tr>
<tr>
<td><strong>Regurgitation</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,545/4,012 (38.5)</td>
</tr>
<tr>
<td><strong>Belching</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,884/4,166 (45.2)</td>
</tr>
<tr>
<td><strong>Empty feeling</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,008/4,039 (25.0)</td>
</tr>
<tr>
<td><strong>Bloating</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,627/4,164 (63.1)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,278/4,139 (30.9)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>327/4,109 (8.0)</td>
</tr>
<tr>
<td><strong>Loss of appetite</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>796/4,119 (19.3)</td>
</tr>
<tr>
<td><strong>Early satiety</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,409/4,121 (34.2)</td>
</tr>
<tr>
<td><strong>Haematemesis</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36/4,091 (0.9)</td>
</tr>
<tr>
<td><strong>Dysphagia</strong></td>
<td></td>
</tr>
<tr>
<td>For liquids</td>
<td>141/4,088 (3.4)</td>
</tr>
<tr>
<td>For solid food</td>
<td>257/3,957 (6.5)</td>
</tr>
</tbody>
</table>

Table 3: Type and frequency of lower gastrointestinal symptoms in respondents experiencing gastrointestinal symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of respondents n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lower abdominal pain</strong></td>
<td></td>
</tr>
<tr>
<td>In general</td>
<td>1,755/4,075 (43.1)</td>
</tr>
<tr>
<td>Postprandial</td>
<td>1,176/3,477 (33.8)</td>
</tr>
<tr>
<td>Pre-prandial</td>
<td>726/3,379 (21.5)</td>
</tr>
<tr>
<td>No reduction after defeation</td>
<td>867/3,338 (26.0)</td>
</tr>
<tr>
<td><strong>Flatulence</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,965/4,193 (70.7)</td>
</tr>
<tr>
<td><strong>Borborygmi</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2,478/4,138 (59.9)</td>
</tr>
</tbody>
</table>

Table 4: Symptom presence in respondents with gastrointestinal symptoms at various age categories

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of respondents n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abnormal defecation</strong></td>
<td></td>
</tr>
<tr>
<td>Black stools</td>
<td>338/3,714 (9.1)</td>
</tr>
<tr>
<td>Blood</td>
<td>187/3,708 (5.0)</td>
</tr>
<tr>
<td>Mucous</td>
<td>557/3,751 (14.8)</td>
</tr>
<tr>
<td>Frequently hard</td>
<td>1,418/3,810 (37.2)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1,330/3,812 (34.9)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1,060/3,859 (27.5)</td>
</tr>
<tr>
<td>Alternately solid or loose</td>
<td>1,939/3,979 (48.7)</td>
</tr>
<tr>
<td>Frequently painful</td>
<td>906/3,818 (23.8)</td>
</tr>
<tr>
<td>Strong urgency</td>
<td>1,541/3,853 (40.0)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>1,143/3,811 (30.0)</td>
</tr>
<tr>
<td>Fatty stools</td>
<td>1,012/3,882 (26.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age categories (years)</th>
<th>18 - 30</th>
<th>31 - 40</th>
<th>41 - 50</th>
<th>51 - 60</th>
<th>61 - 70</th>
<th>≥ 71</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
</tr>
<tr>
<td><strong>Epigastric pain</strong></td>
<td>257/650</td>
<td>238/627</td>
<td>303/799</td>
<td>323/856</td>
<td>196/594</td>
<td>88/305</td>
</tr>
<tr>
<td>In general</td>
<td>(39.5)</td>
<td>(38.0)</td>
<td>(37.9)</td>
<td>(37.7)</td>
<td>(33.0)</td>
<td>(28.9)</td>
</tr>
<tr>
<td>Belching</td>
<td>335/672</td>
<td>288/651</td>
<td>396/870</td>
<td>428/932</td>
<td>278/678</td>
<td>153/349</td>
</tr>
<tr>
<td>(49.9)</td>
<td>(44.2)</td>
<td>(45.5)</td>
<td>(45.9)</td>
<td>(41.0)</td>
<td>(43.8)</td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>486/666</td>
<td>441/647</td>
<td>579/865</td>
<td>583/942</td>
<td>351/678</td>
<td>181/352</td>
</tr>
<tr>
<td>(72.9)</td>
<td>(68.2)</td>
<td>(66.9)</td>
<td>(61.9)</td>
<td>(51.8)</td>
<td>(51.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Heartburn</strong></td>
<td>184/666</td>
<td>223/636</td>
<td>321/822</td>
<td>324/853</td>
<td>200/614</td>
<td>108/314</td>
</tr>
<tr>
<td>In general</td>
<td>(27.8)</td>
<td>(35.1)</td>
<td>(39.1)</td>
<td>(38.0)</td>
<td>(32.6)</td>
<td>(34.4)</td>
</tr>
<tr>
<td><strong>Borborygmi</strong></td>
<td>511/669</td>
<td>411/644</td>
<td>523/864</td>
<td>518/930</td>
<td>331/669</td>
<td>179/350</td>
</tr>
<tr>
<td>(76.4)</td>
<td>(63.8)</td>
<td>(60.5)</td>
<td>(55.7)</td>
<td>(49.5)</td>
<td>(51.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>237/654</td>
<td>194/618</td>
<td>224/808</td>
<td>203/851</td>
<td>111/604</td>
<td>86/311</td>
</tr>
<tr>
<td>(36.2)</td>
<td>(31.4)</td>
<td>(27.7)</td>
<td>(23.9)</td>
<td>(18.4)</td>
<td>(27.7)</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 2

Gastrointestinal symptoms and health-related quality of life

We found that respondents with gastrointestinal symptoms more frequently reported acid-suppressive medication use. Other factors that were also more frequently reported in respondents with gastrointestinal symptoms are depicted in Table 1. After adjustment, female gender (adjusted OR (aOR) 1.59, 95% CI 1.43 - 1.77), asthma/ COPD (aOR 1.47, 95% CI 1.21 - 1.79), use of paracetamol (aOR 1.33, 95% CI 1.20 - 1.47), antidepressants (aOR 1.56, 95% CI 1.22 - 2.00) and use of acid-suppressive medication (antacids aOR 4.22, 95% CI 3.53 - 5.05, H2RAs aOR 9.93, 95% CI 6.72 - 14.7, PPIs aOR 9.29, 95% CI 7.91 - 10.9) remained independently associated with a higher risk for presence of gastrointestinal symptoms (Table 1). Age ≥ 65 years (aOR 0.75, 95% CI 0.65 - 0.87), and use of statins (aOR 0.75, 95% CI 0.61 - 0.93) were independently associated with a lower risk for presence of gastrointestinal symptoms. In the univariable analysis obesity was associated with presence of gastrointestinal symptoms (OR 1.15, 95% CI 1.10 - 1.31), but this association was lost after adjustment (aOR 1.02, 95% CI 0.92 - 1.13).

HEALTH-RELATED QUALITY OF LIFE

The mean utility for health-related quality of life was statistically significantly lower for respondents with gastrointestinal symptoms (0.81, SD 0.21) compared to respondents without gastrointestinal symptoms (0.92, SD 0.14, p < 0.01). This difference was statistically significant (p < 0.01) for all dimensions, and most pronounced for dimensions “pain/discomfort”, “anxiety/depression”, and “usual activities” (Table 5). The gastrointestinal symptom score (VAS) correlated negatively with health-related quality of life (EQ VAS) with a Spearman correlation of -0.57 (p < 0.01), indicating that persons with more severe gastrointestinal symptoms reported a lower health-related quality of life. The following individual symptoms were associated with the lowest health-related quality of life: haematemesis (0.54, SD 0.32), dysphagia for liquid (0.59, SD 0.32) and solid intake (0.62, SD 0.30) and vomiting (0.66, SD 0.30; Supplementary Table 2).

DISCUSSION

We found that 26% of the general population reported gastrointestinal symptoms, with a median duration of eight years. Our study identifies female gender, asthma/ COPD,
use of paracetamol, antidepressants and acid-suppressive medication use as risk factors that were independently associated with a higher prevalence of gastrointestinal symptoms. Older age and statin use protected against gastrointestinal symptoms. Respondents with gastrointestinal symptoms had an impaired health-related quality of life. In comparison to other, older, studies in the field, we found a similar prevalence of gastrointestinal symptoms in the community. This suggests that the effect of time is limited, although there are a plethora of differences between our study and others, most importantly the definitions used to assess prevalence of gastrointestinal symptoms.

We found that females more frequently reported gastrointestinal symptoms, which is in line with other studies regarding gastrointestinal symptoms. In our study, presence of asthma or COPD was an independent risk factor. Presence of asthma is associated with GERD, and recent studies indicate an increased prevalence of GERD symptoms in patients with COPD. Medication use, and especially paracetamol, antidepressants, and acid-suppressive medication contributed significantly to presence of gastrointestinal symptoms in our large population-based survey. The independent association found for paracetamol, probably stems from the use of paracetamol as a panacea for gastrointestinal symptoms. We surmise that this hypothesis also applies to the relation between acid-suppressive medication and gastrointestinal symptoms. The association between antidepressants and gastrointestinal symptoms is complex due to the interactions between: 1) depression and gastrointestinal symptoms; 2) depression and antidepressant use, and 3) antidepressant use and gastrointestinal symptoms.

A total of 11% of our studied population reported PPI use, 2% H2RA use and 6% antacid use. This is much lower than the use of so-called ‘indigestion remedies’ in a study by Jones et al. prior to the PPI era, in which 47-55% of respondents reported any use of this medication class. Use of PPIs was strongly associated with gastrointestinal symptom presence in our study (adjusted OR 9.28, 95% CI 7.91 - 10.9). This can by explained by a combination of indication bias, partial responsiveness on PPI therapy and assessment of both upper and lower gastrointestinal symptom presence. However, the prevalence of gastrointestinal symptoms would be even higher if we would include respondents with acid-suppressive medication without current gastrointestinal symptoms in our prevalence. In a recently published study, the prevalence of upper gastrointestinal symptoms in The Netherlands, the country where our study was performed, was 24%. We found an almost similar prevalence (26%), but we assessed both upper and lower gastrointestinal symptoms. We found that the majority of respondents with gastrointestinal symptoms had both upper and lower gastrointestinal symptoms. Respondents with upper gastrointestinal symptoms have a higher risk for associated lower gastrointestinal symptoms. This is in line with a Japanese study that reported overlap of GERD, functional dyspepsia and IBS in 45% of their studied population. Moreover, in the natural history of functional gastrointestinal disorders many patients frequently switch between upper and lower gastrointestinal symptoms.

We also reported the impact of gastrointestinal symptoms on health-related quality of life. Gastrointestinal symptoms were associated with a disutility of 0.11, which was in line with a disutility for dyspeptic symptoms of 0.09 in another study. Furthermore, we observed that more severe symptoms correlated with a lower health-related quality of life (Supplementary Table 2). By presenting a wide variety of utilities, we have delivered input for cost-utility studies. These studies become more and more important, and are incorporated in clinical guidelines, e.g. by the National Institute for Health and Care and Excellence (NICE).

The major strength of our study is that we examined commonly experienced symptoms in the community by use of a broad definition. Second, in order to attain a representative sample, persons were randomly selected via databases of local authorities without stringent in- and exclusion criteria. Third, we studied gastrointestinal symptoms overall and per symptom instead of in clusters of gastrointestinal symptoms.

Our study design comes with limitations. We cannot exclude response bias, as our response rate was 35%. Response rates in epidemiological studies are declining the last decades and this problem is faced by multiple researchers. A study by Galea et al. describes that a low response rate is not inevitably leading to substantial changes in outcomes. Since our study was performed with postal questionnaires, in comparison to digital surveys, our response rate is actually not that low and still within the range of an acceptable response rate according to Galea et al. Due to concealment we were not able to perform non-responder research. We tried to minimize this bias by inviting all subjects with a personalized cover letter, and we asked explicitly to return the questionnaire, irrespective of presence of gastrointestinal symptoms. Seventy-four percent of all responders did not report the presence of gastrointestinal symptoms. Furthermore, the prevalence of co-morbidities in our study cohort resembles the prevalence in the general population. Therefore, we assume that response bias might be limited. We also cannot exclude that bias was introduced by exclusion of individuals with incomplete information about gastrointestinal symptoms.

The results of our study will refresh awareness among healthcare providers on the high prevalence of gastrointestinal symptoms in the general population. Future research should focus on new targets to effectively treat patients with gastrointestinal symptoms, as we have shown that even many users of acid-suppressive medication still report presence of symptoms. In conclusion, despite increased treatment options and alterations in risk factors, the prevalence of gastrointestinal symptoms in the western community remains high and is associated with a considerable decrease in health-related quality of life.
REFERENCES


27. Likert R. A technique for the measurement of attitudes. Archives of Psychology 1932;140.


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Supplementary Table 1: Prevalence of gastrointestinal symptoms per age category and gender

<table>
<thead>
<tr>
<th>Age categories (years)</th>
<th>18 - 30</th>
<th>31 - 40</th>
<th>41 - 50</th>
<th>51 - 60</th>
<th>61 - 70</th>
<th>≥ 71</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
<td>n/N (%)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 - 30</td>
<td>161/764</td>
<td>201/966</td>
<td>290/1,404</td>
<td>360/1,712</td>
<td>274/1,408</td>
<td>143/766</td>
</tr>
<tr>
<td>31 - 40</td>
<td>(21.1)</td>
<td>(20.2)</td>
<td>(20.7)</td>
<td>(21.0)</td>
<td>(19.5)</td>
<td>(18.9)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 - 30</td>
<td>505/1,513</td>
<td>448/1,512</td>
<td>576/1,886</td>
<td>581/1,932</td>
<td>432/1,493</td>
<td>233/862</td>
</tr>
<tr>
<td>31 - 40</td>
<td>(33.4)</td>
<td>(29.6)</td>
<td>(30.5)</td>
<td>(30.1)</td>
<td>(28.9)</td>
<td>(27.0)</td>
</tr>
</tbody>
</table>

Supplementary Table 2: Impact of individual gastrointestinal symptoms on health-related quality of life

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EQ-SD Utility score Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain</td>
<td>0.74 (0.24)</td>
</tr>
<tr>
<td>In general</td>
<td>0.81 (0.19)</td>
</tr>
<tr>
<td>During daytime</td>
<td>0.72 (0.28)</td>
</tr>
<tr>
<td>At night</td>
<td>0.77 (0.25)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>0.78 (0.23)</td>
</tr>
<tr>
<td>In general</td>
<td>0.78 (0.23)</td>
</tr>
<tr>
<td>During daytime</td>
<td>0.78 (0.23)</td>
</tr>
<tr>
<td>At night</td>
<td>0.77 (0.25)</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>0.77 (0.23)</td>
</tr>
<tr>
<td>Belching</td>
<td>0.78 (0.22)</td>
</tr>
<tr>
<td>Empty feeling</td>
<td>0.75 (0.24)</td>
</tr>
<tr>
<td>Bloating</td>
<td>0.78 (0.22)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.71 (0.26)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.66 (0.30)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>0.67 (0.27)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>0.73 (0.25)</td>
</tr>
<tr>
<td>Haematemesis</td>
<td>0.53 (0.32)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0.59 (0.32)</td>
</tr>
<tr>
<td>For liquids</td>
<td>0.62 (0.30)</td>
</tr>
<tr>
<td>For solid food</td>
<td>0.62 (0.30)</td>
</tr>
</tbody>
</table>
Chapter 2

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EQ-5D Utility score Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abdominal pain</td>
<td></td>
</tr>
<tr>
<td>In general</td>
<td>0.74 (0.24)</td>
</tr>
<tr>
<td>Postprandial</td>
<td>0.75 (0.24)</td>
</tr>
<tr>
<td>Pre-prandial</td>
<td>0.71 (0.28)</td>
</tr>
<tr>
<td>No reduction after defecation</td>
<td>0.73 (0.25)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.79 (0.21)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.78 (0.22)</td>
</tr>
<tr>
<td>Abnormal defecation</td>
<td></td>
</tr>
<tr>
<td>Black stools</td>
<td>0.71 (0.27)</td>
</tr>
<tr>
<td>Blood</td>
<td>0.73 (0.26)</td>
</tr>
<tr>
<td>Mucous</td>
<td>0.73 (0.25)</td>
</tr>
<tr>
<td>Frequently hard</td>
<td>0.76 (0.23)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.76 (0.23)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.73 (0.25)</td>
</tr>
<tr>
<td>Alternately solid or loose</td>
<td>0.78 (0.22)</td>
</tr>
<tr>
<td>Frequently painful</td>
<td>0.70 (0.26)</td>
</tr>
<tr>
<td>Strong urgency</td>
<td>0.76 (0.23)</td>
</tr>
<tr>
<td>Incomplete</td>
<td>0.74 (0.24)</td>
</tr>
<tr>
<td>Fatty stools</td>
<td>0.74 (0.24)</td>
</tr>
</tbody>
</table>

Chapter 3

Open access capture of patients with gastroesophageal reflux disease using an online patient-reported outcomes instrument

Merel M Tielemans
Jan BMJ Jansen
Martijn GH van Oijen

Interactive Journal of Medical Research 2012;1(2):e7
INTRODUCTION

The Internet has gained major influence in the information supply for both physicians and patients in the last decades and has generated new opportunities to study healthcare and diseases.\(^1-4\) Traditionally, medical literature, treatment guidelines, and patient brochures on gastroesophageal reflux disease (GERD) have been available mainly at the general practitioner’s office, and only 5%–30% of patients with GERD consult a general practitioner for their symptoms.\(^5,6\) A recent study found that more than half of online health information seekers searched the Internet without prior medical consultation.\(^6\)

GERD is a chronic relapsing and remitting disorder with heartburn and regurgitation as cardinal symptoms. It is associated with a decreased health-related quality of life.\(^7-9\)

The prevalence of GERD in Western countries is 10%–20\(^%\)\(^5,10\) and the disease accounts for 3%–5% of general practitioner visits.\(^11,12\) The main treatment focus is gastric acid suppression, for which proton pump inhibitors (PPIs) are most effective and are proven to be cost effective.\(^13\)

The majority of persons with GERD symptoms are underreported in the literature, because prior studies regarding GERD were mainly conducted in primary care.\(^14\) Most persons with GERD symptoms do not visit a primary care physician, which is a potential limitation in the understanding of symptom prevalence and treatment response. A German study assessed gastrointestinal symptoms and quality of life via an Internet questionnaire in 5256 individuals between 2002 and 2005.\(^15\) This study concluded that the generated data were in general comparable with non-Internet studies, with the exception that the Internet population was younger. Since then, only a few studies have been conducted on the prevalence of a condition in the general population via the Internet. The majority of Internet-based studies invite participants by email, for example, selected by clinicians or Internet panels,\(^16,17\) thereby preselecting participants.

The aims of the current study were to assess whether it is feasible to study the prevalence and impact of GERD in persons visiting a GERD information website and to identify partial responsiveness to PPI therapy using the GerDQ self-assessment questionnaire. Symptom scores were compared with a validated health-related quality-of-life instrument. We hypothesized that the prevalence of GERD in our Internet population would be high and that a higher GerDQ score would reflect a lower health-related quality of life.

METHODS

STUDY POPULATION

The website www.maagzuur.nl contains information regarding GERD symptoms, possible causes, lifestyle advice, and treatment and diagnostic options. In May 2008, the Dutch translation of the GerDQ self-assessment questionnaire was launched on this website.
and could be completed by all website visitors. After a preparatory period of 6 months, questionnaires completed between 24 November 2008 and 4 May 2011 were included in this study. We excluded respondents younger than 18 and older than 79 years. In the case of duplicate GERD questionnaires—defined as having an identical Internet protocol address, birth year, and gender—we included only the first completed GERD questionnaire. Respondents who scored ≥8 on the GERDQ were subsequently asked to complete the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire.

**THE GERDQ SELF-ASSESSMENT QUESTIONNAIRE**

The GERDQ is a short and validated self-assessment questionnaire that assesses presence of GERD and determines the influence of symptoms on a patient’s daily life. The GERDQ comprises six questions reflecting symptoms in the previous 7 days, and it has been developed with questions from the Reflux Disease Questionnaire, the Gastrointestinal Symptom Rating Scale, and the Gastrointestinal Symptom Scale, all of which are validated disease-specific questionnaires. The GERDQ consists of the following questions referring to the previous week: (1) How often did you have a burning feeling behind your breastbone (heartburn)?; (2) How often did you have stomach contents (liquid or food) moving upward to your throat or mouth (regurgitation)?; (3) How often did you have a pain in the center of the upper stomach?; (4) How often did you have a burning sensation in your throat or mouth (regurgitation)?; (5) How often did you have nausea?; (6) How often did you have difficulty getting a good night’s sleep because of your heartburn and/or regurgitation?; and (6) How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take (such as Maalox)? (see Supplementary Table).

The first two questions (1 and 2) are positive predictors of GERD, where a higher symptom frequency is indicated by a higher score. Questions 3 and 4 address dyspeptic symptoms that decrease the probability of having GERD—that is, they are negative predictors of GERD. The two final questions (5 and 6) assess the impact of symptoms on a person’s daily life and are also positive predictors of GERD. The score on every question ranges from 0 to 3 for the four positive predictors of GERD (0 days is a score of 0; 1 day scores 1; 2–3 days scores 2, and 4–7 days scores 3, or in reversed order for the two negative predictors of GERD). In people who do not use a PPI, a GERDQ score of ≥8 indicates a high probability of having GERD. A cut-off of ≥3 on the GERDQ-impact questions 5 and 6 indicates a high impact of symptoms on a person’s daily life.

We defined partial responsiveness in PPI users as more than 1 day of having heartburn (question 1), regurgitation (question 2), sleep disturbance (question 5), or over-the-counter acid-suppressive medication use (question 6), all during the preceding week. We also analyzed partial responsiveness using a more stringent definition of persistence of heartburn, regurgitation, sleep disturbances, or over-the-counter medication use for at least 4 days during the preceding week. The questionnaire was shown to respondents together with a figure of a human torso with the breastbone and center of the upper stomach being marked.

**QOLRAD QUESTIONNAIRE**

The validated disease-specific QOLRAD questionnaire was developed to monitor health-related quality of life in patients with heartburn and dyspepsia. It contains 25 questions clustered in five domains: emotional distress, sleep disturbance, food and drink problems, physical and social functioning, and vitality. Every question was assessed on a 7-point Likert scale, with a lower score indicating a more severe impact on daily functioning (1 = always, 2 = usually, 3 = frequently, etc, to 7 = never).

**DATA ANALYSIS**

Questionnaires were stored online in a specially designed website content management system (TripTic bv, Eindhoven, The Netherlands). Data were analyzed using SPSS version 16.0 (IBM Corporation, Somers, NY, USA). We calculated total GERDQ score by summing scores for all of the GERDQ questions. The mean age of respondents with high-impact GERD and low-impact GERD were analyzed using the Student’s t-test. The mean age of PPI users with adequate relief and partial responders were also compared by Student’s t-test. We compared dichotomous variables, such as gender, by chi-square (χ²) analysis. Over-the-counter medication use and duration of symptoms were analyzed using descriptive statistics. An overall mean QOLRAD score was calculated by summing scores for all QOLRAD questions, divided by 25 for subgroups of PPI users and non-PPI users. We also calculated a mean score for each domain for respondents with high-impact GERD, low-impact GERD, PPI users with adequate relief, and partial responders to PPI therapy. In respondents with partial responsiveness, we analyzed subgroups of respondents with symptoms persisting at least 4 days per week versus those with less frequent symptoms. Using the Mann-Whitney U test, we compared mean scores in each QOLRAD domain between non-PPI users with low impact and those with high impact, and between PPI users with relief and those with partial response. We also compared mean scores in each QOLRAD domain between partial responders with symptoms persisting at least 4 days per week and those with symptoms persisting at most 3 days per week. A p-value of < 0.05 was considered statistically significant.

**RESULTS**

The GERDQ self-assessment questionnaire was completed 153,415 times between November 2008 and May 2011. After removing duplicate entries (n = 16,447) and excluding respondents aged less than 18 years or 80 years and over (n = 5682), we entered 131,286 GERDQ questionnaires into our analysis (Figure 1). A total of 105,329 respondents (80.23%) reported no use of PPIs and 25,957 respondents (19.77%) reported PPI use (Figure 1).
Capture of patients with GERD via the Internet

Figure 1: Flowchart of participants
GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor, QOLRAD: Quality of Life in Reflux and Dyspepsia

RESPONDENTS WITHOUT PROTON PUMP INHIBITOR USE
The mean age of the 105,329 respondents who did not use PPIs was 41.6 (SD 14) years, and 49.72% (n = 52,369) were male. A total of 37,950 respondents (36.03%) scored <8 on the GerdQ, indicating a low probability for GERD. The remainder (n = 67,379; 64.0%) scored ≥8, of whom half (n = 32,935; 48.88%) reported GERD with a high impact on the respondent’s daily life. Respondents with GERD were older than those without GERD, and the mean age was even higher in respondents with GERD with high impact (Table 1).

Table 1: Baseline characteristics of respondents with and without proton pump inhibitor (PPI) use

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No PPI use</th>
<th>Low-impact GERD (n = 37,950)</th>
<th>High-impact GERD (n = 32,935)</th>
<th>Adequate relief (n = 3,131)</th>
<th>Partial response³ (n = 22,826)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>17,562 (46.28%)</td>
<td>18,035 (52.36%)</td>
<td>16,772 (50.92%)</td>
<td>1,539 (49.15%)</td>
<td>10,132 (44%)</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>39.2 (14)</td>
<td>41.7 (14)</td>
<td>44.3 (14)</td>
<td>49.9 (14)</td>
<td>48.3 (14)</td>
</tr>
<tr>
<td>Age categories (years), n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 – 30</td>
<td>12,937 (34.09%)</td>
<td>9,346 (27.13%)</td>
<td>6,500 (19.74%)</td>
<td>349 (11.15%)</td>
<td>2,719 (12%)</td>
</tr>
<tr>
<td>31 – 40</td>
<td>7,953 (20.96%)</td>
<td>7,096 (20.60%)</td>
<td>6,721 (20.41%)</td>
<td>437 (13.96%)</td>
<td>3,821 (17%)</td>
</tr>
<tr>
<td>41 – 50</td>
<td>8,157 (21.49%)</td>
<td>8,051 (23.37%)</td>
<td>8,252 (25.06%)</td>
<td>717 (22.90%)</td>
<td>5,787 (25%)</td>
</tr>
<tr>
<td>51 – 60</td>
<td>5,833 (15.37%)</td>
<td>6,237 (18.11%)</td>
<td>7,217 (21.91%)</td>
<td>861 (27.50%)</td>
<td>5,815 (26%)</td>
</tr>
<tr>
<td>61 – 70</td>
<td>2,575 (6.79%)</td>
<td>3,038 (8.82%)</td>
<td>3,527 (10.71%)</td>
<td>603 (19.26%)</td>
<td>3,644 (16%)</td>
</tr>
<tr>
<td>71 – 79</td>
<td>495 (1.30%)</td>
<td>676 (1.96%)</td>
<td>718 (2.18%)</td>
<td>164 (5.24%)</td>
<td>1,040 (5%)</td>
</tr>
</tbody>
</table>

GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor
³Partial response: heartburn, regurgitation, sleep disturbance, or over-the-counter medication use for >1 day during the preceding week
⁴p < 0.001 comparing low-impact GERD versus high-impact GERD
⁵p < 0.001 comparing adequate relief versus partial response in PPI users

Of respondents with low-impact GERD, 61.59% (n = 21,215) took over-the-counter medication less than once per week, compared with 8.64% (n = 2,846) of respondents with high-impact GERD (Table 2).
Table 2: Frequency of over-the-counter medication use in respondents with and without proton pump inhibitor (PPI) use

<table>
<thead>
<tr>
<th>Frequency (days/week)</th>
<th>No PPI use</th>
<th>PPI use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No GERD (n = 37,950)</td>
<td>Low-impact GERD (n = 34,444)</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>31,673 (83.46%)</td>
<td>21,215 (61.59%)</td>
</tr>
<tr>
<td>1</td>
<td>4,086 (10.77%)</td>
<td>9,128 (26.50%)</td>
</tr>
<tr>
<td>2 – 3</td>
<td>1,692 (4.46%)</td>
<td>4,101 (11.91%)</td>
</tr>
<tr>
<td>4 – 7</td>
<td>499 (1.31%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

GERD: gastroesophageal reflux disease
\(^a\)Partial response: heartburn, regurgitation, sleep disturbance, or over-the-counter medication use for >1 day during the preceding week

In a subset of respondents we inquired about duration of symptoms. Of those with low-impact GERD, 45.6% (n = 554) reported symptom duration of 1 year or less, while 56.3% (n = 930) of those with high-impact GERD reported symptoms for more than 2 years (Table 3).

Table 3: Duration of symptoms in respondents with and without proton pump inhibitor (PPI) use

<table>
<thead>
<tr>
<th>Duration (months)</th>
<th>No PPI use</th>
<th>PPI use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-impact GERD (n = 1,215)</td>
<td>High-impact GERD (n = 1,652)</td>
</tr>
<tr>
<td>0 – 6</td>
<td>376 (30.96%)</td>
<td>290 (17.55%)(^b)</td>
</tr>
<tr>
<td>7 – 12</td>
<td>178 (14.65%)</td>
<td>213 (12.89%)</td>
</tr>
<tr>
<td>13 – 24</td>
<td>130 (10.70%)</td>
<td>219 (13.26%)</td>
</tr>
<tr>
<td>&gt; 24</td>
<td>531 (43.70%)</td>
<td>930 (56.30%)</td>
</tr>
</tbody>
</table>

GERD: gastroesophageal reflux disease
\(^a\)Partial response: heartburn, regurgitation, sleep disturbance, or over-the-counter medication use for >1 day during the preceding week
\(^b\)\(^c\)\(^d\) \(p < 0.001\) comparing low-impact GERD versus high-impact GERD

A total of 14,028 respondents were eligible for (i.e., GerdQ score ≥8) and invited to complete the QOLRAD questionnaire, of whom 1,231 (8.78%) completed the questionnaire. The total mean QOLRAD score in respondents with GERD with low impact on daily life was 5.77 (SEM 0.04), compared with 5.14 (SEM 0.04) in those with high-impact GERD (\(p < .001\); Figure 2). Quality of life was most impaired in the food/drink domain, and the differences in scores between high-impact and low-impact GERD were most pronounced in sleep disturbances and food/drink problems.
After applying a more stringent definition of partial response, of symptoms persisting at least 4 days per week, we obtained a total of 15,975 individuals (61.54%) reporting partial response. A total of 6238 PPI users were eligible for and invited to complete the QOLRAD questionnaire, of whom 599 (9.60%) completed the disease-specific quality of life questionnaire. The total mean QOLRAD score over all domains was 5.88 (SEM 0.14) in PPI users with adequate relief and 4.62 (SEM 0.05) in PPI users with partial response ($p < .001$; Figure 3).

In both groups of PPI users, scores in the vitality and food/drink domains were lowest, with a consistently lower score in those with partial response. The total mean QOLRAD scores in the two subgroups of partial responders were 5.14 (SEM 0.09) for responders with symptoms persisting at most 3 days per week and 4.43 (SEM 0.06) for responders with symptoms persisting at least 4 days per week ($p < 0.001$ for all domains; Figure 4).

**DISCUSSION**

**PRINCIPAL RESULTS**

We found that the prevalence of GERD in website visitors was high, as over 60% of responders without PPI use scored at or above the predefined cut-off on the GerdQ questionnaire. Of the respondents with GERD who did not use a PPI, 49% reported that their symptoms had a great influence on their daily life, in the form of sleep disturbances, and that they needed over-the-counter medications. This was associated with a decreased health-related quality of life. Almost 90% of PPI users reported persistent GERD symptoms for at least 1 day per week. Partial responders taking PPI therapy had a lower health-related quality of life than those who did not use PPIs and those with adequate symptom relief obtained from PPI therapy.
We used the validated self-assessment questionnaire GerdQ to assess the prevalence of GERD among website visitors. Research via the Internet has several advantages and generates new possibilities. As only a minority of patients with GERD visit a healthcare provider, we can use the Internet to study people who are normally out of the scope of traditional research methods. Another advantage is that missing answers can be directly supplemented during completion of the questionnaire. Data are directly stored electronically, avoiding unreadable handwriting and subsequent mistakes. Data processing via Internet research saves time, especially in studies with many participants. We have shown that it is possible to detect patients with GERD symptoms through a dedicated website. This method can also be used for other conditions. We found that over 150,000 respondents completed the GerdQ questionnaire made accessible online on a health information website, emphasizing the need for disease information on the Internet. However, the skills of the general population to adequately seek health information on the Internet have been shown to be insufficient. These deficiencies varied from problems with opening various common file formats and using hyperlinks embedded in different formats, to problems with appropriately evaluating the information they found.

In our study, only 10% of invited respondents completed the QOLRAD questionnaire. We consider the low response rate on completing the QOLRAD questionnaire to be the main drawback of research via an open access questionnaire. Respondents lack face-to-face contact and miss any relationship with the researchers, reducing their willingness to complete a questionnaire without any expected personal gain. A previous study by McCambridge et al. assessed the effect of length and relevance of questionnaires on completion rates. They found that only relevance, and not length of the questionnaire, influenced response rate. Another limitation of Internet research is that researchers are unaware of the accuracy of the given information. However, this also applies partly to telephone surveys and paper-based questionnaires.

**PARTIAL RESPONSIVENESS IN PROTON PUMP INHIBITOR USERS**

We used the GerdQ self-assessment questionnaire to identify partial responsiveness in PPI users. This is a novel and very promising feature of the GerdQ. We found that almost 90% of all PPI users had heartburn or regurgitation, sleep problems, or over-the-counter acid-suppressive medication use for more than 1 day per week. Of the PPI users, 62% reported persistent symptoms on at least 4 days during the preceding week. Respondents with symptoms persisting at least 4 days per week reported the lowest health-related quality of life in our survey.

A recently published systematic review found that reflux symptoms during PPI therapy persisted in 17%–45% of patients in primary care and the general population. We found a higher proportion of partial responders. This may be due to three independent elements. First, the definitions used in the included articles of the systematic review were not uniform and did not take aspects of quality of life into account. Second, in our study, all website visitors could complete the GerdQ, including those with comorbidity, who are normally excluded from trials. To obtain a maximal treatment effect in clinical trials, respondents with a high risk for decreased efficacy are normally excluded. Third, people with incomplete symptom relief are likelier to search the Internet for more information.

**STRENGTHS AND LIMITATIONS**

Our study has several strengths. We included over 130,000 participants in our study, which is the largest population studied for GERD so far. We used a new, innovative way to collect data. Online data collection can be adequately used in the Netherlands, because more than 85% of Dutch inhabitants already had Internet access in 2008. This is the highest Internet coverage in Europe and would only have increased further during the last 4 years. Using the GerdQ as a promising tool to assess the response of GERD patients to PPI therapy is a novelty. The GerdQ can be used as an easy and quick questionnaire to identify people with an incomplete response. Studies have demonstrated that most physicians presume that PPI therapy is effective in GERD. However, PPIs do not help a significant percentage of patients, which is related to a decreased health-related quality of life.

Our study also has limitations. First, we have to take selection bias into account. Online health information seekers are probably younger and more educated than are people who search for health information offline. We hypothesize that respondents with more severe symptoms might be overrepresented, as they are likely more motivated to search for information. However, a US survey comparing characteristics of offline and online health information seekers found that online seekers reported a better health status. Another aspect of selection bias in our study is that only a minority of respondents completed the QOLRAD questionnaire. A second limitation is that information regarding comorbidity, medical history, or use of other medications was not available. Third, respondents with suspected GERD symptoms did not undergo endoscopy or pH recording. However, previous research demonstrated that the GerdQ has a comparable sensitivity and specificity as a gastroenterologist in diagnosing GERD.

**IMPLICATIONS**

The results of our study have some important implications for clinical practice. Many persons searching the Internet for information about reflux have GERD. This generates new opportunities for using the Internet to recognize and treat GERD. It is possible to detect people with GERD and to advise them at first to adjust their lifestyle and take an over-the-counter medication. If these measures are ineffective, these people can be advised to seek medical treatment. People can also regularly complete the GerdQ self-assessment

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**Definitions:**

- **GERD:** Gastroesophageal reflux disease.
- **PPIs:** Proton pump inhibitors.
- **QOLRAD:** Quality of Life and Reflux Assessment Device.
- **GerdQ:** Gastro-oesophageal reflux disease questionnaire.
questionnaire via the Internet to assess the effectiveness of their treatment. If they are dissatisfied, they can contact a health care practitioner. Most PPI users searching the Internet report persistent symptoms or use over-the-counter medication in addition to PPI treatment. General practitioners and gastroenterologists assume that most patients with GERD are adequately treated, while our study showed the contrary. Health care providers can now use the GerdiQ at every consultation to assess persistent symptoms on PPI therapy and the impact of reflux symptoms on daily life. When necessary, treatment can be adjusted. Further research should investigate the superiority of GerdiQ-assisted practice over standard care. The first study to assess incorporation of the GerdiQ in daily practice was recently published. It compared the GerdiQ with an endoscopy-based approach for diagnosis and initial treatment of GERD, and concluded that using the GerdiQ reduced health care costs with comparable efficacy. We have shown that it is feasible to find patients through a dedicated website for GERD. This concept will also be applicable to other conditions and diseases.

CONCLUSIONS

The GerdiQ self-assessment questionnaire was completed by over 130,000 website visitors. Two-thirds of respondents who did not use PPIs obtained a score suggestive of GERD. The prevalence of partial responsiveness to PPI therapy was high. Respondents reporting a high impact of GERD had a decreased disease-specific health-related quality of life. Identification of people with GERD through a GERD information website has been shown to be feasible.

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Chapter 4

Online follow-up of individuals with gastroesophageal reflux disease using a patient-reported outcomes instrument: results of an observational study

Merel M Tielemans
Martijn GH van Oijen

Accepted for publication in BMC Gastroenterology
Chapter 4 Follow-up of Individuals with GERD via the Internet

BACKGROUND

Gastroesophageal reflux disease (GERD) is a frequent disorder with a prevalence in Western countries of around 10-20%.1-3 As GERD is common in the middle-aged population, it is associated with decreased work productivity, including work absenteeism, leading to substantial indirect healthcare costs.4-7

Despite the high burden of GERD on available healthcare resources, data about the natural course of GERD are scarce.6,9 As ‘second best’, data from placebo groups included in randomized therapeutic trials can be evaluated to develop insight into the natural history of GERD. However, those studies are mainly performed in primary and secondary care, where only around 30% of individuals with GERD symptoms (range: 5 - 56%) ever present with their symptoms.10 Consequently, many individuals that suffer from GERD are not considered for inclusion in those studies.

Use of the Internet is nowadays widespread and many individuals use this source for healthcare information.11-14 A Dutch website with information about GERD was launched and website visitors could complete an online survey about symptoms and proton pump inhibitor (PPI) use. Reasons for visiting a general practitioner or to refrain from consultation were also asked. This model provides a unique opportunity to evaluate a population that have not yet entered the healthcare arena.

The aims of our study are: 1) to prospectively assess GERD symptoms online; 2) to study healthcare practitioner consultation patterns; and 3) to study underlying reasons for healthcare visits.

METHODS

STUDY DESIGN AND PARTICIPANTS

The Dutch website www.maagzuur.nl (“maagzuur” is Dutch for “gastric acid”) contains information regarding GERD symptoms, possible causes, lifestyle advice, diagnostic options and treatment. In May 2008 the Dutch translation of the GerDQ self-assessment questionnaire (Table 1) was launched on this website and could be completed by all website visitors. After a preparatory period of 6 months, questionnaires completed between 5 December 2008 and 2 April 2009 could be included in this study. Follow-up GerDQ questionnaires were sent to all participants (aged 18-79 years) who had a baseline total GerDQ score ≥ 8 and agreed to be contacted again. Questionnaires were sent to eligible respondents after 4, 12 and 24 weeks after completion of the baseline questionnaire. Those who did not complete the first follow-up survey within 7 weeks were excluded to minimize variance. In case of duplicate GerDQ questionnaires entries – defined as: identical IP address, birth year and gender – only the first completed GerDQ questionnaire was included.

Table 1

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>GerDQ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>≥ 8</td>
</tr>
<tr>
<td>Follow-up 1</td>
<td>≥ 8</td>
</tr>
<tr>
<td>Follow-up 2</td>
<td>≥ 8</td>
</tr>
<tr>
<td>Follow-up 3</td>
<td>≥ 8</td>
</tr>
</tbody>
</table>

Background Many individuals with gastroesophageal reflux disease (GERD) never visit their general practitioner. Therefore, prospective data about GERD and its natural history in the general population are scarce. The aims of this study were to assess symptoms over time and consultation reasons in an Internet population with GERD.

Methods Visitors (18-79 years) to a GERD information website who completed the GerDQ self-assessment questionnaire were invited to participate. Follow-up GerDQ questionnaires were sent after 4, 12 and 24 weeks, and those who had a total GerDQ score ≥ 8 and responded to at least the baseline and 4-week questionnaires (within 2-7 weeks) were included in the analyses. Outcome in proton pump inhibitor (PPI) and non-PPI users was classified as symptom improvement, symptom persistence / stable symptoms, or symptom relapse according to GerDQ scores.

Results A total of 403 non-PPI users (mean age 48 years; 40% male) and 304 PPI users (mean age 51 years, 41% male) were included. After 24 weeks, symptom improvement was present in 66% of non-PPI users (45/68) and 8% of PPI users (6/73), while persisting symptoms were reported by 24% (16/68) and 89% (65/73) respectively (baseline symptoms did not influence outcome at 24 weeks). Fifty-five percent of PPI users (116/210) and 37% of non-PPI users (76/207) who intended to visit a healthcare practitioner, performed one or more healthcare visits in the interim. Most frequently reported reason for consultation was persistence of symptoms.

Conclusions GERD symptoms were persistent in the majority of PPI users during our 24-week follow-up, while almost two thirds of non-PPI users reported symptom improvement. Online follow-up of an Internet population with GERD is feasible.
taken into account. Respondents were regarded PPI users as they stated acid-suppressive medication use. The remainder was classified as non-PPI users.

The Medical Ethical Committee of the Radboud University Nijmegen assessed the research proposal of this study and concluded that it could be waived for ethical review, as we did not gather information about participants from other sources (e.g. medical records) and data storage occurred in accordance with Dutch law. For this reason, we did not obtain written informed consent of all participants.

**GERDQ SELF-ASSESSMENT QUESTIONNAIRE**

The GERDQ is a short and validated self-assessment questionnaire that assesses presence of GERD and determines the impact of symptoms on patients’ daily lives.15-16 The GERDQ comprises six questions reflecting symptoms in the previous 7 days, and has been developed with questions from the Reflux Disease Questionnaire (RDQ), the Gastrointestinal Symptom Rating Scale (GSRS), and the Gastrointestinal symptom Scale (GIS), which are all validated disease-specific questionnaires.15-21 The first two questions (1 and 2) are positive predictors of GERD, and a higher score suggests a higher symptom frequency. Questions 3 and 4 address dyspeptic symptoms that lower the probability for GERD, i.e. they are negative predictors of GERD. The two final questions (5 and 6) assess the impact of GERD symptoms on peoples’ lives and are also positive predictors of GERD. The score on every question ranges from 0 to 3 for the four positive predictors of GERD (0 days is a score of ‘0’, 1 day is ‘1’, 2-3 days is ‘2’, 4-7 days is ‘3’, or in reversed order for the two negative predictors of GERD) (Table 1).

**Table 1:** GERDQ Self-assessment questionnaire

<table>
<thead>
<tr>
<th>Symptoms present in the last 7 days</th>
<th>Symptom presence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 days</td>
</tr>
<tr>
<td>Question:</td>
<td></td>
</tr>
<tr>
<td>1. How often did you have a burning feeling behind your breastbone (heartburn)?</td>
<td>0</td>
</tr>
<tr>
<td>2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?</td>
<td>0</td>
</tr>
<tr>
<td>3. How often did you have a pain in the center of the upper stomach?</td>
<td>3</td>
</tr>
<tr>
<td>4. How often did you have nausea?</td>
<td>3</td>
</tr>
<tr>
<td>5. How often did you have difficulty getting a good night’s sleep because of your heartburn and/ or regurgitation?</td>
<td>0</td>
</tr>
<tr>
<td>6. How often did you take additional medication for your heartburn and/ or regurgitation other than what the physician told you to take (such as Maalox)?</td>
<td>0</td>
</tr>
</tbody>
</table>

**OUTCOMES**

Our primary outcome in non-PPI users was “symptom improvement”, which was defined as a GERDQ score < 8 if the respondent scored ≥ 8 on the previous questionnaire. “Stable symptoms” were defined as GERDQ score ≥ 8 at two subsequent completed questionnaires during follow-up. “Relapse” was defined as GERDQ ≥ 8, in case the previous GERDQ score had been < 8.

Our primary outcome in PPI users, “symptom improvement”, was defined as a maximum of one day per week either heartburn (question 1), regurgitation (question 2), sleep disturbance (question 5), or over-the-counter (OTC) acid-suppressive medication use (question 6), all during the preceding week. Persistence of GERD symptoms in PPI users was defined as more than one day per week with either heartburn (question 1), regurgitation (question 2), sleep disturbance (question 5), or OTC acid-suppressive medication use (question 6), during the preceding week. If respondents reported symptoms more than one day per week for at least 2 subsequent GERDQ questionnaires, they fulfilled the criteria for “persistent symptoms”. If the participant reported an increase in symptoms from a maximum of one day per week to at least two times per week, this was defined as “symptom relapse”.

**STATISTICAL ANALYSIS**

Data were analyzed with SPSS version 18.0. Baselines variables for respondents without PPI use and PPI users were assessed with descriptive statistics. Percentages of symptom improvement, stable symptoms, and relapse were assessed separately for PPI and non-PPI users and were calculated with chi-square (χ²) analysis or Fisher exact, whenever appropriate. If one of the follow-up questionnaires was missing, data were compared with the previous completed questionnaire (e.g. if Survey C was missing, data of Survey D and B were compared). Frequencies of heartburn, regurgitation, sleep disturbances and OTC acid-suppressive medication use during follow-up were calculated with frequency tables in respondents without PPI use. Mean symptom frequency within individuals during follow-up was assessed by paired t-tests in non-PPI users. We analyzed respondents according to (non-) PPI use at baseline. Respondents were asked at baseline whether they intended to visit a healthcare practitioner. During follow-up we asked whether they had actually visited a healthcare practitioner. Reasons for consultation were assessed with closed questions and presented in frequency tables. If respondents performed more than one healthcare visit during follow-up, only reasons for the first visit were taken into account. In respondents that did not visit a healthcare provider during follow-up, reasons that were reported in the last completed questionnaire were included and depicted in frequency tables.

Associations between outcome at 24 weeks and GERDQ score at baseline and type of symptom at baseline were analyzed with chi-square (χ²) analyses. We also analyzed the
percentage of respondents that started or stopped their PPI with descriptive statistics. For this analysis, we only took the first medication switch into account. A per protocol analysis was performed, including only those respondents who did not change their use or non-PPI use during the 24-week follow-up. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

A total of 707 respondents met the predefined in- and exclusion criteria and completed the GerdQ between 5 December 2008 and 2 April 2009. (Figure 1). Forty-three percent of respondents (N=304) reported PPI use, the remainder were classified as non-PPI users. Mean age of individuals without PPI use was 48 years (SD 13) and 40% was male. Mean age of PPI users was 51 years (SD 12) and 41% was male.

![Flowchart](image)

In the non-PPI using group, 68 respondents completed follow-up, of which symptom improvement was present in 45/68 respondents (66%) and relapse in 7/68 respondents (10%, Figure 2). Symptoms were persistent in the remaining 16 respondents (24%). In addition, we assessed 4 individual GerdQ questions during follow-up (Table 2).

Figure 1: Flowchart
*Identical IP-address, birth year and gender
PPI: proton pump inhibitor

Figure 2: Symptoms during follow-up in non-PPI users
* P < 0.05
** See Method section for definitions
GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor

After 24 weeks, heartburn or regurgitation for a maximum of one day per week was reported by 44% and 81% of respondents without PPI use, respectively. Mean symptom frequencies of heartburn and regurgitation in non-PPI users significantly declined within individuals during follow-up from 2.21 at baseline to 1.43 at 24 weeks and from 1.20 to 0.77, respectively (both p < 0.01). Mean symptom frequencies of sleep disturbance and OTC use in non-PPI users declined from 1.52 to 1.20 (p = 0.30) and from 1.58 to 1.23 (p = 0.67), respectively.
Follow-up of individuals with GERD via the Internet

Table 2: Individual symptoms during follow-up in respondents without PPI use

<table>
<thead>
<tr>
<th>Symptom frequency</th>
<th>0 days</th>
<th>1 day</th>
<th>2 - 3 days</th>
<th>4 - 7 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn during the preceding week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>25/403 (6.2)</td>
<td>46/403 (11.4)</td>
<td>152/403 (37.7)</td>
<td>180/403 (44.7)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>59/403 (14.6)</td>
<td>84/403 (20.6)</td>
<td>142/403 (35.2)</td>
<td>118/403 (29.3)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>23/140 (16.4)</td>
<td>40/140 (28.6)</td>
<td>41/140 (29.3)</td>
<td>36/140 (25.7)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>15/68 (22.1)</td>
<td>15/68 (22.1)</td>
<td>23/68 (33.8)</td>
<td>15/68 (22.1)</td>
</tr>
<tr>
<td>Regurgitation during the preceding week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>124/403 (30.8)</td>
<td>136/403 (33.7)</td>
<td>82/403 (20.3)</td>
<td>61/403 (19.4)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>130/403 (32.6)</td>
<td>125/403 (31.0)</td>
<td>98/403 (24.6)</td>
<td>44/403 (10.9)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>61/140 (43.6)</td>
<td>40/140 (28.6)</td>
<td>26/140 (18.6)</td>
<td>13/140 (9.3)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>35/68 (51.5)</td>
<td>20/68 (29.4)</td>
<td>10/68 (14.7)</td>
<td>3/68 (4.4)</td>
</tr>
<tr>
<td>Sleep disturbance during the preceding week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>81/403 (20.1)</td>
<td>108/403 (26.8)</td>
<td>136/403 (33.7)</td>
<td>78/403 (19.4)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>116/403 (28.6)</td>
<td>96/403 (23.8)</td>
<td>120/403 (29.8)</td>
<td>71/403 (17.6)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>49/140 (35.0)</td>
<td>36/140 (25.7)</td>
<td>34/140 (24.3)</td>
<td>21/140 (15.0)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>19/68 (27.9)</td>
<td>19/68 (27.9)</td>
<td>21/68 (30.9)</td>
<td>9/68 (13.2)</td>
</tr>
<tr>
<td>OTC use during the preceding week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (%)</td>
<td>107/403 (26.6)</td>
<td>68/403 (16.9)</td>
<td>117/403 (29.0)</td>
<td>111/403 (27.5)</td>
</tr>
<tr>
<td>4 weeks (%)</td>
<td>106/403 (26.0)</td>
<td>70/403 (17.4)</td>
<td>107/403 (26.6)</td>
<td>120/403 (29.8)</td>
</tr>
<tr>
<td>12 weeks (%)</td>
<td>39/140 (27.9)</td>
<td>30/140 (21.4)</td>
<td>33/140 (23.6)</td>
<td>38/140 (27.1)</td>
</tr>
<tr>
<td>24 weeks (%)</td>
<td>25/68 (36.8)</td>
<td>11/68 (16.2)</td>
<td>16/68 (23.5)</td>
<td>16/68 (25.3)</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor, OTC: over-the-counter

In PPI users who completed follow-up, 65/73 (89%) reported persistence of symptoms, 6/73 (8%) reported symptom improvement and 2/73 (3%) relapse of symptoms (Figure 3). Neither individual symptoms nor GerdQ scores at baseline were associated with symptom improvement at 24 weeks in respondents that did and did not use PPIs. During follow-up, 22% started (n = 89/403) and 17% stopped PPI use (n = 53/304). If we excluded these individuals from our analyses, we found that 69% of individuals without PPI use reported symptom improvement (33/48) at 24 weeks in this ‘per protocol’ analysis. In PPI users, 2 participants (2/61; 3%) reported symptom improvement, and the majority (58/61; 95%) reported persistent symptoms.

Table 3: Reasons for consultation for GERD symptoms

<table>
<thead>
<tr>
<th>Reason for consultation</th>
<th>Non-PPI users n = 95</th>
<th>PPI users n = 134</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD symptom persistence (%)</td>
<td>65 (68)</td>
<td>98 (73)</td>
</tr>
<tr>
<td>Increased GERD symptom severity (%)</td>
<td>34 (36)</td>
<td>54 (40)</td>
</tr>
<tr>
<td>No effect previous treatment (%)</td>
<td>8 (8)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>Impact on daily life (%)</td>
<td>39 (41)</td>
<td>69 (52)</td>
</tr>
<tr>
<td>Someone else advised me to consult (%)</td>
<td>12 (13)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Information (%)</td>
<td>12 (13)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Worried (%)</td>
<td>42 (44)</td>
<td>49 (37)</td>
</tr>
<tr>
<td>Anxiety for serious cause (%)</td>
<td>19 (20)</td>
<td>40 (30)</td>
</tr>
<tr>
<td>Other reason (%)</td>
<td>2 (2)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

GERD: gastroesophageal reflux disease, PPI: proton pump inhibitor
*Respondents could report more than one reason
For non-PPI users, worries (44%) and impact on daily life (41%) were also frequently mentioned. In PPI users, impact on daily life (52%), and increased GERD symptom severity (40%) were frequently described reasons. The most reported reason to refrain from consultation was insufficient GERD symptom severity in non-PPI users (44%), and in PPI users (21%, Table 4).

Table 4: Reasons to refrain from a healthcare provider visit for GERD symptoms

<table>
<thead>
<tr>
<th>Reason to refrain from a healthcare provider visit for GERD symptoms</th>
<th>Non-PPI users n = 308</th>
<th>PPI users n = 170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectation of decreasing GERD symptoms (%)</td>
<td>79 (26)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>Insufficient GERD symptom severity (%)</td>
<td>136 (44)</td>
<td>35 (21)</td>
</tr>
<tr>
<td>Confidence in life style changes (%)</td>
<td>105 (34)</td>
<td>36 (21)</td>
</tr>
<tr>
<td>Over-the-counter medication use (%)</td>
<td>104 (34)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Do not want to take medication (%)</td>
<td>24 (8)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Ahead of diagnosis (%)</td>
<td>9 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Do not rely on the doctor (%)</td>
<td>6 (2)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Do not make time to visit healthcare provider (%)</td>
<td>71 (23)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Other reason (%)</td>
<td>27 (9)</td>
<td>80 (47)</td>
</tr>
<tr>
<td>I do not know anymore (%)</td>
<td>62 (2)</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>

PPI: proton pump inhibitor, GERD: gastroesophageal reflux disease
*Respondents could report more than one reason

**DISCUSSION**

We found that 66% of the individuals without PPI use reported symptom improvement at the end of follow-up at 24 weeks. In contrast, only 8% of PPI users reported symptom improvement at the end of follow-up and 89% of PPI users reported persistent symptoms. Limited data are available about long-term effectiveness of PPI therapy in GERD. Short-term studies conclude that 17-45% of patients with GERD do not respond adequately to PPI therapy. Symptom severity was comparable or had improved in the majority of patients after five years in the proGERD study. However, patients included in this proGERD study were recruited from secondary care, whilst our population was not selected by physicians and we did not apply strict inclusion and exclusion criteria. Our population probably also contains respondents with functional upper gastrointestinal symptoms who are less likely to respond to PPI therapy than those with GERD. These factors, in addition to selection bias, could have contributed to the very high rate of persistence of symptoms in PPI users.

As we also focused on a different GERD population, namely Internet users with GERD symptoms without PPI use, we are not able to directly compare our results with others. As second best, we can use placebo responses in clinical trials. A meta-analysis in patients with GERD concluded that the average placebo response was 19%. Follow-up of included studies was short with a maximum of 12 weeks. We found a higher percentage of symptom improvement at 4 and 12 weeks. This can be explained by the inclusion of patients with more severe symptoms in clinical trials and by the definition we used for symptom improvement.

Because many individuals with GERD symptoms refrain from consultations, it is interesting to assess underlying reasons for the decision to visit or not. In a survey among GERD patients in primary care, 52% mentioned that “symptoms too uncomfortable to bear” was the main reason for consultation. The most frequently reported reason for consultation in our study was persistence of GERD symptoms (68% in non-PPI users, 73% in PPI users). Worries about their symptoms were reported by 44% of non-PPI users and 37% of PPI users. Fear is frequently thought to be one of the most important reasons for seeking help, but we were not able to confirm this assumption.

We used the 6-item GerdQ self-assessment questionnaire for follow-up of GERD. The GerdQ appears to be a very promising tool to assess GERD symptoms in a structured, easy way and it is increasingly being used in clinical practice. A recently published study compared a treatment-algorithm based on the GerdQ with common practice of upper endoscopy and if indicated, pH metry in patients with GERD symptoms without any alarm signs. Use of the GerdQ approach was associated with a decrease in healthcare expenses, but had a comparable efficacy. We believe that our data adds to the total, diverse population of individuals with GERD, of which only a minority visits healthcare practitioners. We were able to demonstrate how GERD symptoms evolve on and off PPI treatment. However, including respondents online is associated with limitations, most importantly selection bias. We faced a high dropout rate, probably related to the noncommittal attitude of an online questionnaire and the fact that we asked respondents to complete a total of 4 questionnaires during follow-up. We also do not have additional information about the medical history, comorbidity and reports of any additional investigations, such as upper endoscopy. We therefore cannot exclude that we included individuals with other diagnoses than GERD, or with concomitant diseases in addition to GERD. Another limitation is that we did not question the type and dose of PPI and the duration of use.

**IMPLICATIONS**

Our study has implications for clinical practice. We have shown that it is feasible to use the GerdQ self-assessment questionnaire in PPI users to assess response to acid-suppressive therapy over time. We observed that two thirds of non-PPI users had symptom...
improvement after 24 weeks. This supports the guidelines wherein the first treatment step is lifestyle advice.26,27 Effectiveness of lifestyle interventions has never been systematically studied, but in specific individuals these measures appear to be successful. In addition, our respondents reported confidence in lifestyle interventions (Table 4). When symptoms persist after lifestyle interventions, PPIs can be prescribed.

Our unique approach of online incorporation and follow-up of individuals with GERD demonstrates that the Internet can be used to trace individuals with specific symptoms. The follow-up via the Internet can be used as complementary method to the traditional routes. The communication in our study was one directional, but we will foresee an increase in online health platforms with direct patient-physician communication by e-mail, blog, or message services.

CONCLUSIONS

We found in our 24-week follow-up study via the Internet, that more than half of the respondents without PPI use reported symptom improvement. However, the vast majority of PPI users reported persistence of symptoms. The most frequently mentioned reason for healthcare visits was persistence of symptoms. Based on our results, we support the use of the GerdQ to assess GERD symptoms and we agree with current guidelines that PPI prescription is not the first treatment step when patients present with symptoms suggestive of GERD. We have shown that online follow-up of an Internet population with GERD is feasible.

REFERENCES

Part 2

Determinants of gastrointestinal symptoms
Chapter 5

Identification of NSAID users at risk for gastrointestinal complications:

a systematic review of current guidelines and consensus agreements

Merel M Tielemans
Ties Eikendal
Jan BMJ Jansen
Martijn GH van Oijen

Drug Safety 2010; 33: 443-453
ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most often used drugs worldwide. Numerous NSAID users are at risk for developing gastrointestinal complications. The purpose of this review was to identify and stratify risk factors for gastrointestinal complications in NSAID users documented in guidelines and consensus agreements, and to collect recommendations regarding over-the-counter (OTC) NSAID use. To facilitate this, a PubMed search from 1 January 1999 until 1 March 2009 was performed, resulting in the inclusion of 9 English-language guidelines in our analysis. Risk factors were defined as ‘definite’ if mentioned in all guidelines; otherwise they were defined as ‘controversial’ risk factors.

‘Definite’ risk factors were a history of (complicated) peptic ulcer disease, older age (cut-off range: 60-75 years), concomitant anticoagulant or corticosteroid use and multiple NSAID use, including low-dose aspirin (acetylsalicylic acid). ‘Controversial’ risk factors were high-dose NSAID use, concomitant clopidogrel or selective serotonin reuptake inhibitor use, history of gastrointestinal symptoms, rheumatoid arthritis disability and cardiovascular disease. Infection with Helicobacter pylori was identified as an additive risk factor. Risk factors in OTC NSAID users were difficult to identify in the current literature. Risk factors were not all uniformly present in analyzed guidelines and consensus agreements. We identified a history of (complicated) peptic ulcer disease, older age, concomitant anticoagulant or corticosteroid use and multiple NSAID use, including low-dose aspirin, as definite gastrointestinal risk factors in NSAID users.

INTRODUCTION

NSAIDs are amongst the most frequently prescribed drugs, but their use can be aggravated by adverse effects.1-4 The most commonly reported adverse effects are gastrointestinal, cardiovascular and renal complications. Gastrointestinal adverse effects range from gastrointestinal complaints without visible mucosal lesions at endoscopy to serious gastrointestinal bleeding.5 The prevalence of upper gastrointestinal complaints varies between 5% and 50% of patients receiving traditional and cyclooxygenase-2 (COX-2) selective NSAIDs.6-8 Common symptoms are epigastric pain, heartburn, nausea, regurgitation, bloating and diarrhoea.9 About 1-2% of NSAID users acquire admission to a hospital for serious complications, such as gastric perforation and bleeding, both of which are associated with a high mortality rate.10,11

A frequently employed method to minimize gastrointestinal risk associated with NSAID use is co-prescription of a gastroprotective agent, such as a proton pump inhibitor (PPI) or misoprostol.12-20 This strategy, however, is only cost-effective in NSAID users at high gastrointestinal risk.21 Therefore, several guidelines and consensus agreements were published that designate patients at risk for gastrointestinal complications.12-20 This distinction is based on patient-related risk factors. Guidelines and consensus agreements are not uniform in discussing risk factors or in otherwise attributing the importance of risk factors. Some risk factors are undisputed by authors of analyzed guidelines and consensus agreements whereas others are considered more controversial.

Another issue of concern is gastrointestinal risk in the growing population of over-the-counter (OTC) NSAID users.17 OTC NSAID use is often propagated by general physicians and specialists, but is seldom adequately monitored. A questionnaire-based study performed in Italy by Motola et al. showed that 23% of 2,738 randomly selected subjects had used NSAIDs in the previous week, of which 44% was bought OTC.22 No gastrointestinal complication prevention studies in OTC users have yet been reported. As a consequence, evidence-based guidelines do not recognize the potential gastrointestinal risk in OTC NSAID users. The growing OTC consumption of NSAIDs could well contribute to the incidence of gastrointestinal adverse effects and therefore should be addressed.

The aim of this study is to systematically review guidelines and consensus agreements identifying NSAID users, including those using prescribed NSAIDs and those obtaining NSAIDs OTC, who are at risk for gastrointestinal events. The emphasis of this review will be on individual risk factors for gastrointestinal adverse effects, the role of OTC availability and the recognition of these in guidelines and consensus agreements.
METHODS

LITERATURE SEARCH
We conducted a structured search in PubMed to identify English-language clinical guidelines or consensus agreements regarding risk management of gastrointestinal adverse events in NSAID users, with an emphasis on risk factors and OTC use. Publications from 1 January 1999 until 1 March 2009 were included. If a group of authors published more than one guideline, only the most recent was included.

In the search strategy, the following subject headings and keywords were used: "Anti-Inflammatory Agents, Non-Steroidal [MeSH]" or "nonsteroidal anti-inflammatory drugs" or "NSAID" and "guideline" or "consensus". The following limits within PubMed were used: published in the last 10 years, Humans, Meta-Analysis, Practice Guideline, Consensus Development Conference. The reviewers (MT and TE) then individually assessed the relevancy of all abstracts corresponding with the remaining titles, and excluded abstracts for the following reasons: (1) not concerning gastrointestinal risk factors during NSAID use; (2) not written in English; and (3) no guideline or consensus agreement. From selected abstracts, full papers were reviewed and were only rejected if they (1) made no reference to gastrointestinal risk factors, or (2) were neither guidelines nor consensus agreements. Remaining manuscripts were independently assessed by the reviewers and included if they contained information regarding consideration of gastrointestinal risk factors in the management of NSAID users. Disagreements were adjudicated by discussion and consensus between the two primary reviewers and a third-party arbiter (MvO).

OUTCOMES
Our main interest was to identify common gastrointestinal risk factors among included guidelines and consensus agreements. For this purpose, we conducted a summary table for proper overview of all stated risk factors. Risk factors present among all included papers were defined as ‘definite’ risk factors. Remaining factors were discussed as ‘controversial’ risk factors. Classification, as indicated by the authors, of guidelines included was adopted. OTC use was often not fully incorporated in guidelines; therefore, all statements regarding OTC NSAIDs were collected and presented in a separate table.

RESULTS
A total number of 224 studies were found, of which 215 articles were excluded in two selection procedures. The main reason for exclusion was no mention of a guideline or consensus agreement (Figure 1). Two articles were not written in English; the remaining nine papers were scrutinized by systematic review. Characteristics of included studies are shown in Table 1.

Table 1: Studies included in the review

<table>
<thead>
<tr>
<th>Study</th>
<th>Year published</th>
<th>Specialization</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanza et al.</td>
<td>2009</td>
<td>Gastroenterology</td>
<td>USA, Hong Kong,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ireland</td>
</tr>
<tr>
<td>Bhattach et al.</td>
<td>2008</td>
<td>Cardiology, Gastroenterology</td>
<td>USA</td>
</tr>
<tr>
<td>Chan et al.</td>
<td>2008</td>
<td>Gastroenterology</td>
<td>Hong Kong, USA</td>
</tr>
<tr>
<td>Rostom et al.</td>
<td>2008</td>
<td>Gastroenterology</td>
<td>Canada</td>
</tr>
<tr>
<td>American College of</td>
<td>2008</td>
<td>Rheumatology</td>
<td>USA</td>
</tr>
<tr>
<td>Rheumatology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tangen and Thomson</td>
<td>2006</td>
<td>Gastroenterology, Family medicine</td>
<td>Canada</td>
</tr>
<tr>
<td>Wilcox et al.</td>
<td>2006</td>
<td>Gastroenterology, Rheumatology</td>
<td>Canada, USA,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiology, Internal medicine</td>
<td>Spain</td>
</tr>
<tr>
<td>Dubois et al.</td>
<td>2004</td>
<td>Medical researcher</td>
<td>USA</td>
</tr>
<tr>
<td>Schoenfeld et al.</td>
<td>1999</td>
<td>Gastroenterology</td>
<td>USA</td>
</tr>
</tbody>
</table>
DEFINITE RISK FACTORS

Risk factors for gastrointestinal complications in NSAID users present in all analyzed guidelines could be defined as ‘definite’ risk factors. We defined the following risk factors as ‘definite’: history of complicated (defined as peptic ulcer bleeding, obstruction or perforation) and uncomplicated peptic ulcer disease, older age, concomitant anticoagulant use, concomitant corticosteroid use and concomitant low-dose aspirin (acetylsalicylic acid) or multiple NSAID use (Figure 2, Table 2, Table 3). In this review we report on the most discussed variables only - older age and the use of multiple NSAIDs.

Figure 2: Presence of risk factors in analyzed guidelines and consensus agreements

Table 2: Overview presence of risk factors in analyzed guidelines

<table>
<thead>
<tr>
<th>Risk factora</th>
<th>Lanza et al.16</th>
<th>Bhatt et al.13</th>
<th>Chan et al.14</th>
<th>Roston et al.17</th>
<th>Am Coll Rheum12</th>
<th>Targownik and Thomson19</th>
<th>Wilcox et al.10</th>
<th>Dubois et al.15</th>
<th>Schaeftld et al.18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>∆ ≥75</td>
<td>∆ ≥75</td>
<td>∆ ≥70</td>
<td>∆ ≥60-75</td>
<td>∆ ≥75</td>
<td>∆ ≥76</td>
<td>∆ ≥75</td>
<td>∆ ≥76</td>
<td>∆ ≥65</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Complicated PUD</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Uncomplicated PUD</td>
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<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
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<td>A</td>
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<tr>
<td>GI symptoms</td>
<td>NP</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple NSAIDsb</td>
<td>NPA</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>(acetylsalicylic acid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>NPA</td>
<td>A</td>
<td>A</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
</tbody>
</table>

Risk factorsa

- Corticosteroids
- SSRI
- Dose
- Cardiovascular disease
- Severe RA disability
- Additive

Table 3: Risk factors identified in the guidelines

<table>
<thead>
<tr>
<th>Risk factora</th>
<th>Lanza et al.16</th>
<th>Bhatt et al.13</th>
<th>Chan et al.14</th>
<th>Roston et al.17</th>
<th>Am Coll Rheum12</th>
<th>Targownik and Thomson19</th>
<th>Wilcox et al.10</th>
<th>Dubois et al.15</th>
<th>Schaeftld et al.18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
<td>∆</td>
</tr>
<tr>
<td>SSRI</td>
<td>NPA</td>
<td>NP</td>
<td>NPA</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Dose</td>
<td>∆</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>∆</td>
<td>NP</td>
<td>NP</td>
<td>∆</td>
<td>NP</td>
<td>∆</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Severe RA disability</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>∆</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Additive</td>
<td>Helicobacter pylori</td>
<td>∆</td>
<td>∆</td>
<td>NPA</td>
<td>∆</td>
<td>∆</td>
<td>NPA</td>
<td>NP</td>
<td>NPA</td>
</tr>
</tbody>
</table>

Controversial

- High-dose NSAID
- Clopidogrel
- SSRI

Additivec

- Helicobacter pylori infection

NSAID: nonsteroidal anti-inflammatory drug, PUD: peptic ulcer disease, SSRI: selective serotonin reuptake inhibitor

aDefinite risk factor is present in all analyzed guidelines and consensus agreements
bControversial risk factor is not present in all guidelines
cAdditive risk factor is only of importance in patients with a history of peptic ulcer disease
Older age
All included studies regarded older age as definite risk factor, but the exact threshold was not uniform and ranged from 60 to 75 years. Bhatt et al., Rostom et al. and Schoenfeld et al. considered patients to be at high risk if they were aged > 60 years. Age > 65 years was considered a risk factor by Lanza et al., and Dubois et al. Significant increased risk for gastrointestinal complications in patients aged ≥ 70 years was described by Chan et al. The threshold in the guideline of the American College of Rheumatology was 75 years, which is similar to the guideline by Targownik and Thomson, i.e., 76 years and older. Wilcox et al. did not dichotomize risk stratification according to an age threshold; they stated that advancing age increases gastrointestinal risk by about 4% per year.

Multiple NSAIDs and concomitant low-dose aspirin (acetylsalicylic acid)
Intake of more than one type of NSAID was regarded as a risk factor in most guidelines and consensus articles. Some consensus groups considered low-dose aspirin (75-325 mg daily) as a separate risk factor, while others regarded low-dose aspirin as a subtype of traditional NSAIDs. Higher gastrointestinal risk by use of multiple NSAIDs, including concomitant low-dose aspirin, was considered a definite risk factor among all guidelines.

CONTROVERSIAL RISK FACTORS
The guidelines assessed for this systematic review were not uniform for all risk factors. No agreement was present for a history of gastrointestinal symptoms, and the exact role of concomitant clopidogrel therapy, concomitant selective serotonin reuptake inhibitor (SSRI) use and comorbidity.

History of gastrointestinal symptoms
Only two guidelines considered the history of gastrointestinal symptoms as a risk factor for patients receiving NSAID therapy. Upper gastrointestinal symptoms, described as upper abdominal pain or discomfort or increase of symptoms of gastroesophageal reflux disease, should be analyzed according to the methods of Bhatt et al. and Rostom et al., because, according to these authors, a positive history augments the relative risk for gastrointestinal complications.

High-dose NSAID
In many, but not all, analyzed guidelines, a high dose of NSAIDs is a risk factor for gastrointestinal complications; however, the exact definition of high dose was not stated.

Concomitant medication
Concomitant use of several drugs was regarded as a risk factor. As stated before, corticosteroid, anticoagulant and low-dose aspirin use are definite risk factors. Concomitant clopidogrel therapy was regarded a risk factor in three of nine papers, and concomitant SSRI use was mentioned in two guidelines. Clopidogrel was approved in 1998 and since then the number of prescriptions has increased. Concomitant clopidogrel therapy has been recognized as a risk factor in the guidelines of Bhatt et al., Chan et al. (published in 2008) and Rostom et al. (published in 2009). However, the guideline published in 2009 by Lanza et al. did not assess clopidogrel as a risk factor. Concomitant use of SSRIs is mentioned in two guidelines, namely in the guidelines of Rostom et al., and Targownik and Thomson. The latter stated that the evidence of an increased number of complications is weak.

Comorbidity
The presence of rheumatoid arthritis or cardiovascular disease was included as a risk factor in several guidelines and consensus agreements. Severe rheumatoid arthritis was assessed as a risk factor in three guidelines (Rostom et al., American College of Rheumatology and Schoenfeld et al.). According to Schoenfeld et al., rheumatoid arthritis patients are more prone to use multiple and higher dosages of medications. Cardiovascular disease has been described by the same three groups as being a risk factor for gastrointestinal complications. Schoenfeld et al. defined cardiovascular disease as "a history of heart disease". The two other guidelines did not define cardiovascular disease. The clinical consequence of rheumatoid arthritis and cardiovascular disease in patients requiring NSAIDs appears to be independent of the background of the authors.

ADDITIVE RISK FACTOR
Helicobacter pylori
Infection with Helicobacter pylori is a known risk factor for peptic ulcer disease, but the exact role of H. pylori in NSAID-related gastrointestinal complications is not yet clear. Guidelines agree that patients with a history of (complicated) peptic ulcer disease who start NSAID therapy should be tested and treated for H. pylori; however, according to Lanza et al., eradication of H. pylori for secondary prevention of peptic ulcer bleeding alone seems insufficient in long-term NSAID users. This is mainly based on a large, randomized, double-blind clinical trial in H. pylori-positive naproxen users that showed statistically significant more recurrent upper gastrointestinal bleeding in patients treated with H. pylori eradication therapy compared with patients receiving long-term omeprazole (hazard ratio 7.1, 95% CI 1.9 - 27.6).

OVER-THE-COUNTER USE
One of the purposes of this systematic review was to identify recommendations regarding OTC NSAID use. OTC use has been increasing last decennia and is becoming more...
important; however, we found little information about OTC NSAID use in the studied guidelines and consensus agreements. In particular, no information regarding identification of patients at risk for gastrointestinal side effects in OTC users was mentioned. Examples of statements from the literature regarding OTC NSAID use are provided in Table 4.

Table 4: Quotes on over-the-counter (OTC) NSAID use

<table>
<thead>
<tr>
<th>Study</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanza et al.</td>
<td>“It is important to emphasize that physicians are often unaware that patients are self-medicating with low-dose aspirin when they are prescribed an NSAID for pain relief or anti-inflammatory effect.”</td>
</tr>
<tr>
<td>Bhatt et al.</td>
<td>“These agents, both through prescription and over-the-counter (OTC) use, are the most widely used class of medications in the United States.”</td>
</tr>
<tr>
<td>“As the incidence of arthritis complaints increases, the use of prescription and OTC NSAIDs is also expected to increase.”</td>
<td></td>
</tr>
</tbody>
</table>
| “Recommendation: As the use of any NSAID, including COX-2-selective agents and OTC doses of traditional NSAIDs, in conjunction with cardia
c-dose aspirin, substantially increases the risk of ulcer complications, a gastroprotective therapy should be prescribed for at-risk patients.” |
| Rustom et al. | “Nonsteroidal anti-inflammatory drugs are prescribed short term to about 25% of Canadians and long term (defined in this study as ≥ 6 months) to about 4%. However, this underestimates the magnitude of NSAID use as it does not include over-the-counter NSAID users and low-
dose aspirin is extensively used for cardiovascular risk reduction.” |
| Wilcox et al. | “Notably, both NSAID-associated gastrointestinal complications and deaths have been decreasing in recent years, after peaking in 1992. This decrease has been attributed to many factors including the use of lower-dose (particularly over-the-counter) NSAIDs, the decreasing prevalence ...” |
| Dubois et al. | “In the year 2000, US patients received 111,400,000 prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs), at a cost of nearly $5 billion, with an additional $2 billion spent on over-the-counter NSAIDs.” |
| Schoenfeld et al. | “In 1991, the year that naproxen and ketoprofen became available without prescription, an estimated 14 million Americans ingested NSAIDs on a daily basis.” |

DISCUSSION

We found advanced age, history of complicated as well as uncomplicated peptic ulcer disease, concomitant use of multiple NSAIDs (including low-dose aspirin), concomitant use of anticoagulant therapy and concomitant use of corticosteroids to be definite risk factors for a gastrointestinal event in NSAID users. Controversial risk factors were concomitant use of clopidogrel and concomitant SSRI use, comorbidity, a history of gastrointestinal symptoms and high-dose NSAID use. Infection with H. pylori was regarded as an additive risk factor, which was only of importance in patients with a history of (un)complicated peptic ulcer disease.

Although older age was an undisputed risk factor throughout all included guidelines, the exact threshold remains under discussion. In our review, the threshold ranged from 60 to 75 years of age. One guideline noted a linear risk increase of 4 percent per advancing year.26 The choice of an adequate threshold might be influenced by the patient population that the guideline refers to, but we could not identify specific thresholds within medical specializations and therefore attempted to determine other reasons for the wide range of this threshold. Many articles have been published about the cut-off value for advanced age in NSAID users; however, not all of these were cited in the different guidelines. For example, only two references that determined this age cut-off, were used in more than one guideline.26,27 We did not have insights into the reference selection procedures of the included guidelines, therefore the exact reasoning behind the chosen threshold remains unknown.

If medical costs are taken into account, co-prescription of a gastroprotective agent or prescription of a selective COX-2 inhibitor is cost-effective in patients older than 75 years and in patients with a history of (complicated) peptic ulcer disease, independent of their age.26 Logically, costs are lower when the cheapest PPI is prescribed. No therapeutic strategy is currently cost-effective in patients without risk factors.21 Concomitant use of multiple NSAIDs, including low-dose aspirin, was also defined as a definite risk factor. Gastrointestinal adverse effects of low-dose aspirin (75 - 325 mg/day) are mainly attributed to systemic side effects, whereas in high dose NSAID users also local gastric injury is present.26 However, several authors defined low-dose aspirin to be a traditional NSAID and therefore categorize it as multiple NSAID use.16,20 Data are not uniform regarding the risks of solitary NSAID use and the combination of NSAIDs with low-dose aspirin. Relative risk estimations vary, from a two-fold increase for solely low-dose aspirin use20,31 to a six-fold increase when combining NSAIDs and low-dose aspirin.20 Although the number needed to harm is high, the number of patients using the combination of NSAIDs and low-dose aspirin is extensive, subsequently resulting in a large number of gastrointestinal events.13,32
Following the report by Lanza et al., infection with *H. pylori* was regarded as an additive risk factor for gastrointestinal events in NSAID users. Secondary prevention, by testing and subsequently treating *H. pylori* infection in patients with a known history of (complicated) peptic ulcer disease, has proven to be beneficial in NSAID users at high risk for gastrointestinal complications. Eradication of *H. pylori* in high-risk patients before the start of NSAID therapy has shown to reduce the incidence of ulceration; however, eradication therapy of *H. pylori* in long-term NSAID users is inferior to using adequate gastroprotection. When both *H. pylori* and NSAID use are present, the relative risk for gastrointestinal complications of NSAID use is greater than that of infection with *H. pylori* alone, suggesting that NSAIDs play a more dominant role. A study regarding cost-effectiveness demonstrated that *H. pylori* eradication in patients above the age of 50 years was the most effective cost-saving strategy in preventing gastrointestinal complications in NSAID users. In summary, data about the exact role of *H. pylori* in peptic ulcer disease in NSAID users are conflicting and the importance of *H. pylori* in ulcer development in NSAID users is still under debate.

Concomitant use of clopidogrel is a controversial risk factor. Only three included papers mentioned an increased gastrointestinal risk. Although clopidogrel was only approved in 1998, its gastrointestinal adverse effects are well known. Combination of different antithrombotics act in a synergistic manner, suggesting that the combination of a traditional NSAID with clopidogrel will also lead to an increased risk of gastrointestinal complications. Recently, studies regarding the interaction between clopidogrel and PPIs were published. Concomitant PPI use seems to abolish the cardiovascular protective effects of clopidogrel. With this knowledge, the European Medicines Agency made a public statement about this interaction in May 2009 and discourages concomitant use of a PPI and clopidogrel-containing medicines unless absolutely necessary. This further complicates the preventive strategies as PPIs are the primary choice for gastroprotection in this population. Concomitant use of SSRIs is also a controversial risk factor. A recently published meta-analysis by Loke et al. demonstrated that the odds ratio for upper gastrointestinal hemorrhage in patients using SSRIs alone was 2.36 (95% CI 1.44 - 3.85) compared with 6.33 (95% CI 3.40 - 11.8) in patients using NSAIDs and concomitant SSRIs. The increased risk of concomitant SSRI therapy on gastrointestinal events in patients using NSAIDs should be taken into account by any physician as both drugs are often prescribed together. At present, SSRIs as risk factor might be controversial as it only has been recently identified and will need further exploration.

Individual NSAIDs have different gastrointestinal toxicity profiles and, therefore, do not lead to comparable amounts of gastrointestinal complications. Ibuprofen is a traditional NSAID with the lowest gastrointestinal risk, whereas piroxicam has an almost four-fold higher risk of gastrointestinal complications compared with ibuprofen. Also, the dosage of NSAIDs is of importance in gastrointestinal complications. For example, it is possible that the low risk associated with ibuprofen found in the majority of studies where it is included may be because a low dose is usually used. A study by Guthmann et al. indicated that the risk of upper gastrointestinal bleeding and perforation with ibuprofen at a daily dose of 1500 mg or less was 1.2 compared with 5.8 at daily doses above 1500 mg. The definition of high dose was not stated in the included guidelines and consensus agreements.

Comorbidity was recognized as a risk factor. Depending on specialization, authors found severe rheumatoid arthritis, a history of any cardiovascular event, heart failure and diabetes mellitus to be risk factors; however, patients experiencing any of the mentioned diseases may use more, and higher, doses of medication. Association of comorbidity with an increased risk of a gastrointestinal event in patients using NSAIDs could therefore well be secondary to concomitant multiple drug use. Cardiovascular risks of NSAID use, with emphasis on selective COX-2 inhibitors, are widespread. OTC availability contributes to the growing consumption of NSAIDs. Guidelines and consensus agreements on the role of OTC NSAIDs were therefore reviewed in order to examine risk factors in this specific but large group of NSAID users. We hypothesize that gastrointestinal risk in individuals using OTC NSAIDs may well be similar to patients using prescribed NSAIDs. Both lower dosing and less frequent use could contribute to a lower gastrointestinal risk than that of prescribed NSAIDs. On the contrary, gastrointestinal risk could be higher because of multiple NSAID use if a NSAID is prescribed by a physician in addition to OTC use or individuals might not adhere to recommended dosages or cautions. However, although the risk is difficult to assess, it may not be discarded because of the large numbers of NSAIDs used. OTC NSAID use is difficult to control by a pharmacist; therefore, perhaps guidelines with directive focus on OTC use should primarily be aimed at pharmacists in order to identify patients at risk. This may explain why reviewed guidelines did not address OTC use.

We advise physicians to carefully interrogate for possible OTC NSAID use if a patient is at increased risk for gastrointestinal complications. Moreover, if physicians recommend (OTC) NSAID use, they should always consider gastrointestinal risk factors and take these into account prior to their recommendation. Other options include switching to paracetamol (acetaminophen) or co-prescription of a gastroprotective agent. No studies are currently available that have examined gastrointestinal risks in naïve OTC NSAID users. To elucidate this issue, a large clinical trial should be performed wherein OTC NSAID users with definite gastrointestinal risk factors would randomly be assigned to either of the following options: 1) switching to (OTC) paracetamol; 2) co-prescription of a PPI; and 3) no intervention. However, this is not feasible because of ethical concerns with an increased mortality due to gastrointestinal complications in older patients. Without the results of a prospective study, recommendations regarding OTC NSAID use in patients at risk for gastrointestinal complications are not evidence-based.
In this systematic review, we only included guidelines and consensus agreements published in English, which could possibly account for selection bias as the reviewed guidelines are all derived from Western countries, which are accountable for the vast majority of NSAID use; therefore, guidelines and consensus agreements mostly originate from these countries. Another limitation of this study might be our interpretation of the authors’ interpretation of analyzed guidelines and consensus agreements. A systematic review is as strong as its individual components; however, interpretation of numerous studies is the limitation of all (systematic) reviews. In contrast, although scientific sources of most guidelines and consensus agreements concur, authors’ interpretations lead to different recommendations, as shown in this article. This systematic review puts these interpretations into perspective. We included articles that used differing methodology, such as panel discussions and opinion articles, with the terms ‘guideline’ or ‘consensus’ present in the title. Although methodology is not consistent, the management of patients using NSAIDs in many countries worldwide is largely dependent on discussed guidelines and consensus agreements.

In conclusion, we reviewed guidelines and consensus agreements on risk factors for gastrointestinal events in patients using NSAIDs and identified a history of (complicated) peptic ulcer disease, older age (cut-off age ranging from 60 to 76 years), concomitant anticoagulant use, concomitant corticosteroid use, and multiple NSAID use, including low-dose aspirin, as undisputed definite gastrointestinal risk factors in NSAID users. Several controversial risk factors, including concomitant clopidogrel and SSRI use, require further research. Finally, we found an absence of recommendations regarding OTC NSAIDs in studied guidelines and consensus agreements. OTC NSAID use should be addressed and considered by physicians in the identification of patients at risk for a gastrointestinal event.

REFERENCES


Chapter 6

Gastrointestinal symptoms in NSAID users in an ‘average-risk population’:
results of a large population-based study in randomly selected Dutch inhabitants

Merel M Tielemans
Leo GM van Rossum
Ties Eikendal
Jeroen Jaspers Focks
Robert JF Laheij
Jan BMJ Jansen
Martijn GH van Oijen

In revision
INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed drugs worldwide. In the Netherlands, NSAIDs were prescribed to 3 million users in 2009 (Data from the Dutch Foundation for Pharmaceutical Statistics (SFK)) and in the United States, prescriptions for generic ibuprofen and naproxen almost reached 40 million in 2009. Over-the-counter (OTC) NSAID use is also widespread, as an Italian survey suggested that approximately 15% of the general population had used OTC NSAIDs in the previous week. The prevalence of upper gastrointestinal symptoms in users of prescribed NSAIDs varies widely from 5% to 50%. Studies regarding these adverse events have frequently been performed in selected populations, such as in patients with rheumatoid arthritis. Data about gastrointestinal symptoms in OTC NSAID users are scarce. Some studies conclude that side effects of OTC NSAIDs are comparable to paracetamol and placebo, while others report that prevalence of gastrointestinal symptoms in OTC NSAID users is twice as high compared to non-NSAID users. In addition to gastrointestinal symptoms, NSAID use is associated with gastrointestinal bleeding. In order to prevent gastrointestinal complications in NSAID users at risk for gastrointestinal complications (e.g. those at advanced age), guidelines advise to apply a gastroprotective strategy. However, purchase of OTC NSAIDs occurs outside the scope of pharmacies and healthcare practitioners and careful consideration for the need of gastroprotection may not be present. Therefore, the aims of this study are to assess 1) gastrointestinal symptoms in prescribed and OTC NSAID users, and 2) PPI co-prescription rates in NSAID users at increased risk for gastrointestinal complications via a cross-sectional study in the general population.

METHODS

STUDY POPULATION

We sent 51,869 questionnaires by mail to a sample of the Dutch population in December 2008. We included returned questionnaires from December until the end of March 2009. Invited subjects were 18 years or older and randomly selected from municipal databases of five different municipalities selected on their geographical location in The Netherlands, in order to gather a representative sample of the Dutch population. We excluded returned questionnaires with missing elements that were part of (1) the primary outcome measure, (2) all individual gastrointestinal symptoms, (3) missing of all baseline characteristics, or (4) questionnaires with unreadable medication.

ABSTRACT

Aims Nonsteroidal anti-inflammatory drug (NSAID) use is widespread and associated with gastrointestinal symptoms and complications. The aims of this study are to assess: 1) gastrointestinal symptoms in users of prescribed and over-the-counter (OTC) NSAIDs, and 2) proton pump inhibitor (PPI) co-prescription rates in NSAID users at increased risk for gastrointestinal complications.

Methods Surveys were sent to a randomly selected sample of the adult Dutch general population in December 2008. Questions included demographics, gastrointestinal symptoms, medication use and comorbidity. Main outcome measure was presence of gastrointestinal symptoms.

Results A total of 18,317 surveys returned (response rate 35%), of which 16,758 surveys were eligible for analysis. Of these, 3,233 participants (19%) reported NSAID use. NSAID users more frequently reported gastrointestinal symptoms than persons not using NSAIDs (33% vs. 24%, p < 0.01). Respondents that specified on prescription NSAID use (n = 683) were older, reported more comorbidity, and experienced more gastrointestinal symptoms (41%) compared to OTC users (n = 894, 33%, p < 0.01). This difference was not statistically significant after adjustment for confounders (aOR 0.99, 95% CI 0.71 - 1.37). In respondents with an increased gastrointestinal risk profile PPI co-prescription rates were 51% for on prescription users and 25% for OTC users.

Conclusions Prevalence of gastrointestinal symptoms was high in both prescribed and OTC NSAID users, emphasizing the side effects of both types of NSAIDs. PPI co-prescription rates in NSAID users at risk for gastrointestinal complications were low.
The Medical Ethical Committee of the Radboud University Nijmegen assessed the proposal of this study and concluded that it could be waived for ethical review, as questionnaires were returned and stored anonymously, and (non-)responders would not be contacted again. For this reason, we did not obtain written informed consent of all participants.

QUESTIONNAIRE

The questionnaire was specifically designed for collection of demographic information, gastrointestinal symptoms, medication use, and health-related quality of life and has been used before.\(^{13-15}\) Participants were asked whether they suffer from gastrointestinal symptoms in general, and if so, they were asked about the presence of 26 specific gastrointestinal symptoms such as nausea, early satiety, bloating, constipation and diarrhea. Severity of these gastrointestinal symptoms was assessed on a seven-point Likert scale (0 = absent, 1 = almost absent, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe) over the four preceding weeks.\(^{16}\) A symptom was considered to be present if participants scored \(\geq 2\) on the Likert scale.

Our primary outcome was the presence of gastrointestinal symptoms in general assessed by: “Do you experience gastrointestinal complaints?” and had to be answered with either “yes” or “no”. Secondary outcome was type of gastrointestinal symptoms experienced in the preceding four weeks.

Participants were asked to report currently used medication and to specify whether it was prescribed or bought OTC. When NSAID users reported a history of (complicated) peptic ulcer disease, concomitant use of systemic corticosteroids, anticoagulants or antiplatelet therapy, or were aged \(\geq 65\) years, we defined them as participants with high risk for gastrointestinal complications in accordance with current guidelines.\(^{12}\)

We defined excessive alcohol consumption as 14 units or more a week for women and 21 units or more a week for men.\(^{17}\) Body mass index (BMI in kg/m\(^2\)) was categorized in \(< 25\) (normal weight) and \(\geq 25\) (overweight or obese).\(^{18}\) Participants were asked to report their current smoking habits without specification of the amount of tobacco used.

STATISTICAL ANALYSIS

Data were analyzed using Statistical Package for the Social Sciences (SPSS), version 16.0 (IBM Corporation, New York, United States). Frequency tables with characteristics of the participants were presented according to NSAID use. Pearson’s chi-square (\(\chi^2\)) analysis was used to compare categorical variables between users of prescribed and OTC NSAIDs, and to assess symptoms according to PPI use. Concomitant medication use in users of prescribed and OTC NSAIDs was also assessed using Pearson’s chi-square (\(\chi^2\)) test. Continuous variables were compared with Student’s t-test or the Mann-Whitney U method whenever appropriate. In respondents with gastrointestinal symptoms, specific symptoms were provided using frequency tables. Individual symptoms between prescribed and OTC NSAID users were compared with Pearson’s chi-square (\(\chi^2\)) test. We performed univariable logistic regression and subsequent multivariable logistic regression analysis to correct for confounders. Covariates were included if baseline characteristics differed significantly between on prescription and OTC NSAID users, or if factors were known to be associated with gastrointestinal symptoms in NSAID users from the literature. Odds ratios and 95% confidence intervals were stated. A \(p\)-value < 0.05 was assumed to be statistically significant.

RESULTS

Of the 51,869 surveys sent, a total of 18,317 were returned (response rate 35%). Seven hundred forty-two surveys returned unopened to sender for various reasons and after exclusion for previously described reasons (\(n = 817\)), a total of 16,758 questionnaires could be included in the analysis (Figure 1). Nineteen percent of all participants (\(n = 3,233\)) report NSAID use. NSAID users reported more frequently gastrointestinal symptoms (\(n = 1,076\) of 3,233; 33%) compared with non-NSAID users (\(n = 3,239\) of 13,525; 24%; \(p < 0.01\)).

![Figure 1: Flowchart](image)

*Some respondents met more than one exclusion criterion

NSAID: nonsteroidal anti-inflammatory drug, OTC: over-the-counter
A total of 1,656 NSAID users did not specify whether their NSAID use was on prescription or OTC. Of the remainder, six hundred eighty-three (43%) respondents reported on prescription NSAID use and 894 participants (57%) use of OTC NSAIDs. Users of prescribed NSAIDs were older (mean 51 years, SD 15) compared with OTC users (mean 40 years, SD 14, p < 0.01), more often overweight (58% vs. 39%, p < 0.01) and more frequently reported comorbidity (33% vs.10%, p < 0.01; Table 1).

Prevalence of gastrointestinal symptoms was 41% in users of prescribed NSAIDs and 33% in OTC users (OR 1.41, 95% CI 1.15 - 1.74; Table 2). Reported symptom frequencies are depicted in Figures 2a and 2b. On prescription NSAID users significantly more often reported nocturnal epigastric pain (36% vs. 23%, p < 0.01), nocturnal heartburn (33% vs. 24%, p = 0.03), vomiting (15% vs. 9%, p = 0.03) and pre-prandial lower abdominal pain (29% vs. 21%, p = 0.03) compared to OTC NSAID users. All other reported symptoms were comparable between groups. After adjustment with multivariable analysis, the odds ratio was not statistically significant (adjusted OR 0.99, 95% CI 0.71 - 1.36; Table 2).

Table 1: Population characteristics

<table>
<thead>
<tr>
<th>Respondents without NSAID use</th>
<th>Respondents that did not specify type of NSAID use</th>
<th>On prescription NSAID users</th>
<th>OTC NSAID users</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 13,525</td>
<td>n = 1,656</td>
<td>n = 683</td>
<td>n = 894</td>
<td></td>
</tr>
<tr>
<td>Mean age (aSD)</td>
<td>50 (16)</td>
<td>50 (16)</td>
<td>51 (15)</td>
<td>40 (14)</td>
</tr>
<tr>
<td>Age ≥ 65 years (%)</td>
<td>2,706 (20)</td>
<td>332 (23)</td>
<td>123 (18)</td>
<td>37 (4)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>7,188 (55)</td>
<td>971 (60)</td>
<td>452 (68)</td>
<td>621 (71)</td>
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<tr>
<td>Body mass index ≥ 25 kg/m² (%)</td>
<td>6,064 (46)</td>
<td>824 (51)</td>
<td>381 (58)</td>
<td>347 (59)</td>
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<tr>
<td>Smoking (%)</td>
<td>2,302 (17)</td>
<td>341 (21)</td>
<td>124 (19)</td>
<td>162 (18)</td>
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<tr>
<td>Excessive alcohol usea (%)</td>
<td>1,312 (13)</td>
<td>174 (15)</td>
<td>71 (17)</td>
<td>66 (10)</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease (%)</td>
<td>677 (5)</td>
<td>123 (8)</td>
<td>55 (8)</td>
<td>31 (4)</td>
</tr>
<tr>
<td>Peptic ulcer bleeding (%)</td>
<td>217 (2)</td>
<td>39 (2)</td>
<td>17 (3)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>695 (5)</td>
<td>113 (7)</td>
<td>46 (7)</td>
<td>23 (3)</td>
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<tr>
<td>Rheumatoid arthritis (%)</td>
<td>458 (3)</td>
<td>120 (7)</td>
<td>168 (25)</td>
<td>27 (3)</td>
</tr>
<tr>
<td>Asthma / COPD (%)</td>
<td>811 (6)</td>
<td>128 (8)</td>
<td>53 (8)</td>
<td>52 (6)</td>
</tr>
</tbody>
</table>

*Comparison between on prescription and OTC NSAID users

Table 2: Unadjusted and adjusted odds ratios for presence of gastrointestinal symptoms in NSAID users

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>On prescription vs. OTC</td>
<td>1.41 (1.15 - 1.74)</td>
<td>0.99 (0.71 - 1.38)</td>
</tr>
<tr>
<td>Ageb</td>
<td>1.00 (0.99 - 1.01)</td>
<td>0.98 (0.97 - 0.99)</td>
</tr>
<tr>
<td>Female</td>
<td>2.01 (1.58 - 2.55)</td>
<td>2.69 (1.92 - 3.77)</td>
</tr>
<tr>
<td>Body mass index ≥ 25 kg/m²</td>
<td>1.27 (1.03 - 1.56)</td>
<td>1.38 (1.01 - 1.87)</td>
</tr>
<tr>
<td>History of peptic ulcer disease</td>
<td>4.99 (3.20 - 7.77)</td>
<td>3.07 (1.66 - 5.66)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.82 (1.40 - 2.35)</td>
<td>2.34 (1.63 - 3.36)</td>
</tr>
<tr>
<td>Excessive alcohol usec</td>
<td>1.12 (0.77 - 1.63)</td>
<td>0.74 (0.47 - 1.18)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>1.83 (1.35 - 2.47)</td>
<td>0.94 (0.54 - 1.66)</td>
</tr>
<tr>
<td>Asthma/COPO</td>
<td>1.61 (1.08 - 2.39)</td>
<td>1.30 (0.70 - 2.41)</td>
</tr>
<tr>
<td>PPIs</td>
<td>4.07 (3.14 - 5.29)</td>
<td>7.16 (4.59 - 11.17)</td>
</tr>
<tr>
<td>H2RAs</td>
<td>6.14 (3.10 - 12.16)</td>
<td>6.44 (2.64 - 15.68)</td>
</tr>
<tr>
<td>Antacids</td>
<td>2.46 (1.79 - 3.38)</td>
<td>2.59 (1.66 - 4.02)</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>2.05 (1.74 - 2.39)</td>
<td>0.66 (0.12 - 3.48)</td>
</tr>
<tr>
<td>Low-dose aspirind</td>
<td>0.99 (0.67 - 1.44)</td>
<td>0.81 (0.46 - 1.41)</td>
</tr>
</tbody>
</table>

aAdjusted for all variables depicted in this table
bPer advancing year
cExcessive alcohol use is defined as 14 units or more a week for women and 21 units or more a week for men

USE OF ACID-SUPPRESSIVE MEDICATION IN NSAID USERS

For our analyses regarding gastroprotection, we found that concomitant PPI use was reported by 227 on prescription NSAID users (33%), compared with 81 OTC NSAID users (9%; Table 3). These numbers were 114 (51%) and 28 (25%) respectively in the subgroup of participants with an increased risk for gastrointestinal complications based on international guidelines for gastroprotection (p < 0.01).

We performed subgroup analyses in NSAID users that used any form of acid suppression (PPI, H2RA or antacid) in addition to their NSAID use. In this analysis, we did not find any statistically significantly differences (adjusted OR 0.76, 95%CI 0.41 - 1.39). We also performed a subgroup analysis in NSAID users that did not use PPIs, H2RAs or antacids. We did not find any differences in gastrointestinal symptom prevalence between on prescription NSAID users (n = 384) and OTC NSAID users (n = 713) (adjusted OR 1.01, 95% CI 0.67 - 1.52).
Gastrointestinal symptoms in NSAID users

**Figure 2a:** Upper gastrointestinal symptoms in respondents reporting gastrointestinal symptoms

- Respondents without NSAID use
- On prescription NSAID users
- Over-the-counter NSAID users

*p < 0.05

NSAID: nonsteroidal anti-inflammatory drug

**Figure 2b:** Lower gastrointestinal symptoms in respondents reporting gastrointestinal symptoms

- Respondents without NSAID use
- On prescription NSAID users
- Over-the-counter NSAID users

*p < 0.05

NSAID: nonsteroidal anti-inflammatory drug
We compared type of gastrointestinal symptoms in respondents with gastrointestinal symptom presence, according to PPI and type of NSAID use. Epigastric pain during daytime (58% vs. 42%, p = 0.02), heartburn in general (51% vs. 34%, p < 0.01), heartburn during daytime (52% vs. 35%, p < 0.01), and regurgitation (54% vs. 36%, p < 0.01) were more frequently reported in prescribed NSAID users with concomitant PPI use than prescribed NSAID users without PPI use. Epigastric pain during daytime (60% vs. 41%, p = 0.02), nocturnal epigastric pain (39% vs. 19%, p < 0.01), heartburn in general (52% vs. 30%, p < 0.01), heartburn during daytime (48% vs. 31%, p = 0.03) and regurgitation (53% vs. 38%, p = 0.04) were more frequently reported in OTC NSAID users with PPI use compared with OTC NSAID users without PPI use.

**DISCUSSION**

Nineteen percent of our random sample of the Dutch general population reported NSAID use. This was associated with a higher prevalence of gastrointestinal symptoms compared to participants not using NSAIDs. After adjustment for confounders, prevalence of gastrointestinal symptoms did not differ between participants reporting NSAID use on prescription compared to OTC. This indicates that NSAID use was an independent risk factor for occurrence of gastrointestinal symptoms, irrespective of on prescription or OTC use. PPI co-prescription was frequently absent in NSAID users at increased risk for gastrointestinal complications.

Previously conducted randomized controlled trials about NSAIDs in OTC dosages concluded that maximum OTC doses naproxen and ibuprofen were not associated with increased side effects.\(^5,19\) However, included participants were healthy volunteers, and the duration of exposure was short. A recent review article supported the safety of OTC NSAIDs.\(^20\) We found a higher prevalence of gastrointestinal symptoms in NSAID users, but our study included a wide variety of individuals, while most previous studies in OTC NSAID users included a more homogenous – relatively low risk – population, leading to less gastrointestinal symptoms. Therefore, extrapolation of the former results to the general population needs to be done with caution.

We studied PPI co-prescription in NSAID users at increased risk for gastrointestinal complications. Gastroprotection rates in users of prescribed NSAIDs range between 44-70% and are mainly based on either prescription numbers generated from medical records or reimbursement schemes by health insurance databases.\(^21,26\) The PPI co-prescription rate in NSAID users at risk in our study was at the lower end of this range, but we used self-reported, and probably more reliable, data. We also analyzed gastroprotection rates in OTC NSAID users, as the risk on gastrointestinal complications is up to 3-4 times increased compared to placebo\(^20,26\), and found that only 25% of those at risk concomitantly used PPIs.

It is a challenge to improve the current low gastroprotection rates in OTC NSAID users at risk. If NSAIDs are prescribed it is clear that the responsibility – to identify patients at risk and co-prescribe gastroprotection – lies with the attending physician, but with OTC NSAID use this is less clear. NSAID OTC packages could be marked with warning signs and depict risk factors for gastrointestinal complications, but consumers of OTC medication frequently do not read the package inserts.\(^24\) We also could instruct sellers of OTC NSAIDs to systematically ask presence of gastrointestinal risk factors and subsequently advice to concomitantly use a PPI. In practice this will be difficult to implement. The alternative, a NSAID-PPI combination pill, is not yet available OTC.

Based on the results of our cross-sectional study, we are unable to confirm the role of PPIs in reducing NSAID-associated gastrointestinal symptoms, which has been demonstrated before.\(^29-32\) PPI use is independently associated with gastrointestinal symptom presence in our survey due to confounding by indication.

The major strength of our study is that we performed a direct comparison between users of prescribed and OTC NSAIDs in the general population, which is a mixture of different gastrointestinal risk categories. Secondly, our data regarding NSAID use and subsequent gastroprotection are not based on prescription or sales rates, but on self-reported use.
Our population survey also has limitations. Approximately half of respondents that reported NSAID use did not specify whether used NSAIDs were on prescription or OTC. Respondents that did not specify their NSAID use reported a lower frequency of gastrointestinal symptoms, which may have led to an overestimation of gastrointestinal symptom prevalence in our cohort of NSAID users, because NSAID users that developed side effects could have been more likely to remember this previous NSAID use and additional details. Second, the response rate of our study was 35% and respondents experiencing gastrointestinal symptoms may have been more susceptible to return the questionnaire. To minimize this bias, all participants were invited with a personalized cover letter, asked explicitly to return the questionnaire, indifferent of gastrointestinal symptoms. The two types of bias described above, recall bias and selection bias, both may have influenced our primary outcome. Due to our study design we were not able to test this in non-responders or respondents who returned an incomplete questionnaire.

Another limitation is that we are uninformed whether PPIs were primarily prescribed for gastroprotection, or for another indication as gastroesophageal reflux disease (GERD) or dyspepsia. Another study found that a history of NSAID intolerance, GERD and dyspepsia were all significantly associated with use of gastroprotective agents in NSAID users.23 As we were unaware of the reason for PPI co-prescription, we also did not question our population for the indication, dose and duration of NSAID use. Adequate gastroprotection in NSAID users at risk for gastrointestinal complications can be achieved by PPI co-prescription or by prescription of a COX-2 selective NSAID. Due to the nature of our questionnaire we were not able to separately assess COX-2 selective NSAID users and nonselective NSAID users. This may have led to some underestimation of adequate gastroprotection rates in users of prescribed NSAIDs. However, PPI co-prescription is the most frequently adapted strategy in NSAID users at risk for gastrointestinal complications in daily practice.

In all questionnaire-based studies the results rely on fairness and adequacy of the answers reported by participants. We assume our questionnaire has been completed properly, but we cannot rule out that some misclassification has occurred. At last, we cannot rule out that NSAID users are unaware of the gastrotoxic nature of this medication29,33,34 and used these analgesics for dyspeptic symptoms.

Use of prescribed NSAIDs will probably increase in future with prolonged life expectancy and concomitant rheumatic complaints. Continuing increase of self-medication and promotion of OTC NSAID use by general practitioners and specialists will also contribute to increased NSAID use. Our study documents that OTC NSAID use is associated with gastrointestinal symptoms. A study, published in 2001, found that physicians do no question patients on a regular basis OTC medication use.35 We suppose that awareness regarding OTC use has improved since due to incorporation of questions about OTC use in guidelines regarding gastrointestinal symptoms.26,37

The major medical implication of our study is that awareness of physicians about the risks of OTC NSAID medication use should be further improved. Second, we would recommend policy makers to either stimulate adequate gastroprotection in OTC NSAID users at risk or to limit free availability of OTC NSAIDs or preferably both. In conclusion, nineteen percent of participants reported NSAID use. Prevalence of gastrointestinal symptoms was increased in both prescribed and OTC NSAID users. Physicians should be aware of the extensive use of OTC NSAIDs in the general population and ask patients presenting with gastrointestinal symptoms about OTC drug use. An advice to stop any avoidable use of OTC NSAID should be considered prior to or at least in addition to prescribing gastroprotective medication.
REFERENCES


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Chapter 7

Esomeprazole relieves upper gastrointestinal symptoms in high-risk and average-risk NSAID users in daily clinical practice:
results from an open-label study

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Martijn GH van Oijen
Chris JJ Mulder
Kees J Vos
Willem F Lems

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Chapter 7

ABSTRACT

Objective To investigate whether esomeprazole can provide relief for nonsteroidal anti-inflammatory drug (NSAID)-associated upper gastrointestinal symptoms in patients at different gastrointestinal risk.

Methods A multicentre, prospective, open-label study was conducted, wherein NSAID users visiting their general practitioner for upper gastrointestinal symptoms were asked to participate. Patients were treated with 20 mg esomeprazole and treatment effect was evaluated within 8 weeks. Response was defined as a maximum of one day per week with gastrointestinal symptoms during the last week of treatment. Partial response was defined as more than 50% improvement in the number of days per week with symptoms compared with baseline. Patients not meeting the above-mentioned criteria were classified as nonresponders. Patients who completely responded were compared with partial responders and nonresponders and were analyzed according to their baseline gastrointestinal risk.

Results A total of 1,042 patients (mean age 57 years, SD 15, 43% male) were analyzed. Complete response, partial response and nonresponse were achieved in 57%, 24% and 19% of the patients, respectively. Similar response was seen in average-risk and high-risk patients (58% and 56%, p = 0.46) and in nonselective NSAID and selective cyclooxygenase-2 users (57% and 53%, p = 0.32).

Conclusion Esomeprazole (20 mg) improved NSAID-associated upper gastrointestinal symptoms. Baseline gastrointestinal risk did not influence esomeprazole effectiveness.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often prescribed for treatment of pain and inflammation but are associated with gastrointestinal side-effects ranging from life-threatening peptic ulcer bleeding to minor dyspeptic symptoms.1-4 Side effects are the most common reason for NSAID discontinuation and have a considerable negative impact on quality of life.5,6 Compared with nonselective NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors induce fewer ulcers and complications, although the prevalence of gastrointestinal symptoms in patients using selective COX-2 inhibitors is still 5-50%.2,3,7,8 In treatment guidelines9-10, acid-suppressive drugs are recommended as a first-line treatment option for acid-related upper gastrointestinal symptoms. Proton pump inhibitors (PPIs) are the most potent agents for suppressing intragastric acidity, but remarkably, only few studies have examined upper gastrointestinal symptoms as a primary endpoint in NSAID users.11-13 Studies by Hawkey et al.11-15 and Scheiman et al.16 have already shown the ability of esomeprazole (20 and 40 mg) to reduce gastrointestinal symptoms in NSAID users in large randomized clinical trials with stringent in- and exclusion criteria (NASA1 and SPACE1, VENUS, PLUTO). However, the actual effectiveness of PPIs on gastrointestinal symptoms in daily practice has not been thoroughly investigated. In most clinical trials, patients with risk factors for gastrointestinal complications, for example, concomitant low-dose aspirin or systemic corticosteroid use, are frequently excluded, but such patients are encountered in clinical care.14 In NSAID users, treatment of upper gastrointestinal symptoms using a PPI may prevent complications such as peptic ulcer disease.12,14-17 If gastrointestinal symptoms are reduced by PPI therapy, then patients might also be more adherent to treatment after gastroprotection guidelines. This hypothesis is untested to date, but, if true, it may contribute to closing of the gastroprotective gap.

We hypothesize that PPI therapy will relieve upper gastrointestinal symptoms in NSAID users in daily clinical practice. Second, we want to assess symptom relief in both average-risk and high-risk patients, as NSAID users at risk might experience less symptom relief. Therefore, the aim of this study was to investigate whether PPI therapy can reduce upper gastrointestinal symptoms in NSAID users in daily clinical practice and to assess response to PPI therapy in several subgroups according to risk for gastrointestinal complications.

METHODS

STUDY DESIGN AND PATIENTS

In this multicentre prospective open-label study, patients were included between October 2006 and June 2007. Follow-up visits were performed until August 2007. A total of 162
general practitioner centres in the Netherlands participated. NSAID users who visited their general practitioner with heartburn, regurgitation, nausea and/or bloating were asked to participate. Patients were included if they used NSAIDs for more than 2 days a week for at least one week and if NSAID treatment was expected to continue during study follow-up. Because patients presented to a general practitioner with varying durations of symptoms, no minimal symptom period was defined. The effect of PPI treatment was evaluated once within 8 weeks. Exclusion criteria included: age less than 18 years, a history of gastrooesophageal reflux disease (GERD), and use of PPI and/or H₂-receptor antagonist in the month preceding the study. Eligible patients were prescribed 20mg esomeprazole once daily.

OUTCOMES

Patients were questioned at baseline visit and at follow-up visit within 8 weeks. Demographic factors, type and dosage of NSAID, indication, risk factors for gastrointestinal complications and the severity of upper gastrointestinal symptoms were recorded. More than one indication could be reported per NSAID prescription. Symptoms assessed were heartburn, regurgitation, bloating and nausea. The number of days that patients experienced one or more of these symptoms during the last week was assessed. Severity of gastrointestinal symptoms was measured on a four-point Likert scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), and a mean symptom score was calculated. Primary outcome was treatment response, which was defined as a maximum of 1 day per week with gastrointestinal symptoms during the last week of treatment. A patient not meeting this definition would be a partial or non-responder. Partial response was defined as more than 50% improvement in the number of days per week with symptoms compared with baseline. Patients not meeting the above-described criteria were classified as non-responders.

The general practitioner was also asked to score the patient as “high-risk” or “average-risk” for gastrointestinal events on the basis of global physician assessment. Thereafter, the gastrointestinal risk profile of a patient was assessed more structurally using the following individual risk factors: aged 65 years or above, a history of (complicated) peptic ulcer disease, and co-prescription of low-dose aspirin, anticoagulants or systemic corticosteroids.

SAFETY

During the study general physicians recorded all serious adverse events and adverse events resulting in discontinuation of esomeprazole treatment. A serious adverse event was defined as an adverse event leading to death, life-threatening situation, unscheduled hospital admission or extension of a hospital stay, a permanent or severe disability, or a necessity for an intervention to prevent permanent loss of function or permanent damage to any part of the body.

SAMPLE SIZE

Sample size calculation was based on the assumption that mean improvement in gastrointestinal symptom score would be different between patients at high gastrointestinal risk and those with average risk, favouring patients at average gastrointestinal risk. The expected difference was estimated to be 0.25 with a standard deviation of 1.45 and was derived from a former study. To detect this difference with 80% power and 5% significance level, 530 patients were needed in each group. With an expected dropout of 15%, a total of 1,220 had to be included. We assumed that high and average risks were equally divided in the patients visiting the general practitioner for gastrointestinal symptoms who were taking NSAIDs.

STATISTICAL ANALYSIS

Analyses were carried out using Statistical Package for the Social Sciences, version 18.0 (IBM Corp., Somers, New York, USA). Baseline characteristics were analyzed using standard descriptive statistics. Response of upper gastrointestinal symptoms (primary endpoint) was analyzed as follows: mean symptom scores at baseline were compared with scores after treatment using paired t-tests for all individual symptoms. Baseline characteristics were then compared between responders and all others using chi-square (χ²) tests for intergroup comparisons of dichotomous data and analysis of variance for continuous data. The correlation between the number of days between two general practitioner visits and the likelihood of response was compared using Spearman’s correlation coefficient.

We carried out multivariable analysis to assess the factors that were associated with response to PPI therapy. Logistic regression analysis was also carried out to assess the adjusted impact of several risk factors (older age, history of peptic ulcer disease and concomitant low-dose aspirin, corticosteroid, selective serotonin reuptake inhibitor and anticoagulant use) on the general practitioners’ estimation of patients’ gastrointestinal risk. Odds ratios and 95% confidence intervals (CIs) were stated. A p value < 0.05 was assumed to be statistically significant.

ETHICAL ISSUES

This study was conducted according to the Declaration of Helsinki and international standards of good clinical practice. The trial had been registered at Clinicaltrials.gov (NCT00524329).
RESULTS

A total of 1,233 patients were included in this study. In all, 191 patients were excluded from the study; 29 patients did not meet the inclusion criteria; 1 did not return for the second visit; and 161 patients did not visit the general practitioner within the defined period for analysis following the first visit. In comparison with patients included in the study, excluded patients were younger (mean age 54 years, SD 16 years). No differences were found in comorbidities or in the use of concomitant medications. Treatment outcome was analyzed in the remaining 1,042 patients (mean age 57 years, SD 15 years, 43% male). Almost one-third of the patients were aged above the age of 65 years (Table 1).

Table 1: Population characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 1,042</th>
</tr>
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<tbody>
<tr>
<td>Mean age in years (±SD)</td>
<td>57.2 (15.4)</td>
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<tr>
<td>≥ 65 years (%)</td>
<td>365 (35)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>447 (43)</td>
</tr>
<tr>
<td>History of peptic ulcer disease (%)</td>
<td>104 (10)</td>
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<td>Concomitant medication (%)</td>
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<tr>
<td>High risk according to GPR² (%)</td>
<td>604 (58)</td>
</tr>
</tbody>
</table>

COX-2: cyclo-oxygenase-2; GP: general practitioner; NSAID: nonsteroidal anti-inflammatory drug; SSRI: selective serotonin reuptake inhibitor

The most frequently reported indication for NSAID use was nonspecific musculoskeletal pain (50%), followed by osteoarthritis (34%). The most often prescribed NSAID was diclofenac (46%), followed by ibuprofen (30%) and naproxen (15%) (Table 2). More than 10% of used NSAIDs were purchased over-the-counter. A total of 104 patients changed their NSAIDs during the study period, of which 87 patients reported the names of both NSAIDs; most patients (73 of 87) changed NSAIDs within the nonselective NSAID group. Seven patients changed within the COX-2 selective group and 7 patients switched from a nonselective NSAID to COX-2 selective or vice versa. A total of 604 patients (58%) were assessed to be at high risk for gastrointestinal complications by the general practitioner.

Table 2: Number of patients (%) using NSAIDs at the time of inclusion

<table>
<thead>
<tr>
<th>Type of NSAID</th>
<th>Total n = 1,042</th>
<th>OTC (%) n = 122 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonselective</td>
<td>n = 896 (%)</td>
<td>n = 122 (12%)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>413 (46)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>266 (30)</td>
<td>96 (36)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>137 (15)</td>
<td>19 (14)</td>
</tr>
<tr>
<td>Diclofenac/misoprostol</td>
<td>45 (5)</td>
<td>-</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>12 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>11 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Other³</td>
<td>12 (1)</td>
<td>2 (17)</td>
</tr>
<tr>
<td>Selective COX-2 inhibitor</td>
<td>n = 146 (%)</td>
<td>n = 9</td>
</tr>
<tr>
<td>Etodolacib</td>
<td>63 (43)</td>
<td>-</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>45 (31)</td>
<td>-</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>37 (25)</td>
<td>-</td>
</tr>
<tr>
<td>Valdecoxib</td>
<td>1 (0)</td>
<td>-</td>
</tr>
</tbody>
</table>

COX-2: cyclo-oxygenase-2; NSAID: nonsteroidal anti-inflammatory drug; OTC: over-the-counter

Some patients reported more than one indication

Patients at high risk for gastrointestinal complications according to the general practitioner

Figure 1 presents the effects of esomeprazole on NSAID-associated gastrointestinal symptoms. Overall, 81% of patients responded positively to PPI therapy, of which 24% responded partially. Nineteen percent of patients were nonresponders.
Characteristics of patients, such as completely responding, partially responding and non-responders on esomeprazole therapy, are shown in Table 3. Patients at higher risk for gastrointestinal complications (according to the general practitioner) were older (mean age 61 years, SD 15) compared with patients with average risk (mean age 52 years, SD 14). Sex distribution was similar between the two subgroups. The outcome in patients at higher risk for gastrointestinal complications was comparable with the other groups: in the high-risk group, response and non-response was 56% and 18%, respectively, compared with 58% and 20% in the average-risk group.

In addition, response in nonselective NSAID users compared to selective COX-2 inhibitor users was similar: response 57%, partial response 29%, and non-response 14% in nonselective NSAID users compared to 53%, 30%, and 17% in COX-2 selective NSAID users, respectively. No relationship was found between the number of days between two general practitioner visits and the likelihood of response (r = -0.001, p = 0.964). The most frequently reported symptom at inclusion was heartburn (93%) with a mean symptom score of 1.77 (SD 1.5). After treatment, upper gastrointestinal symptom scores improved significantly for all studied domains: heartburn, regurgitation, bloating and nausea (p < 0.01 for all comparisons).

Multivariable regression analysis demonstrated that selective serotonin reuptake inhibitor use (adjusted odds ratio (aOR) 0.49, 95% CI 0.33 - 0.74), anticoagulant use (aOR 0.56, 95% CI 0.32 - 0.98), heartburn (aOR 0.83, 95% CI 0.70 - 0.99) and regurgitation (aOR 0.84, 95% CI 0.72 - 0.99) at baseline were associated with a higher response rate to PPI therapy (Table 5).
Table 4: Overall symptom improvement in terms of mean symptom score

<table>
<thead>
<tr>
<th>Symptom score</th>
<th>Before esomeprazole treatment</th>
<th>After esomeprazole treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heartburn, mean (SEM)</td>
<td>1.77 (0.026)</td>
<td>0.35 (0.017)*</td>
</tr>
<tr>
<td>Regurgitation, mean (SEM)</td>
<td>1.19 (0.028)</td>
<td>0.23 (0.015)*</td>
</tr>
<tr>
<td>Bloating, mean (SEM)</td>
<td>1.42 (0.028)</td>
<td>0.31 (0.016)*</td>
</tr>
<tr>
<td>Nausea, mean (SEM)</td>
<td>1.06 (0.028)</td>
<td>0.16 (0.019)*</td>
</tr>
</tbody>
</table>

SEM: standard error of mean

*p < 0.01

Table 5: Multivariable analysis of factors associated with response vs. partial and no response combined

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>0.91 (0.70 - 1.18)</td>
<td>0.93 (0.70 - 1.24)</td>
</tr>
<tr>
<td>Female</td>
<td>0.81 (0.63 – 1.04)</td>
<td>0.81 (0.62 – 1.05)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>0.97 (0.59 - 1.58)</td>
<td>1.19 (0.71 – 2.00)</td>
</tr>
<tr>
<td>SSRI</td>
<td>0.47 (0.32 – 0.73)</td>
<td>0.49 (0.33 – 0.74)</td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>0.93 (0.64 – 1.36)</td>
<td>1.73 (0.91 – 3.29)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>0.75 (0.54 – 1.06)</td>
<td>0.56 (0.32 – 0.98)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.99 (0.70 – 1.40)</td>
<td>1.07 (0.73 – 1.56)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.69 (0.43 – 1.11)</td>
<td>0.79 (0.45 – 1.36)</td>
</tr>
<tr>
<td>History of PUD</td>
<td>1.07 (0.71 – 1.62)</td>
<td>1.34 (0.86 – 2.10)</td>
</tr>
<tr>
<td>Use of COX-2 selective NSAID</td>
<td>0.85 (0.60 – 1.21)</td>
<td>0.86 (0.59 – 1.25)</td>
</tr>
</tbody>
</table>


General practitioners were asked to estimate whether patients were at high risk for gastrointestinal complications. A patient reporting a history of (complicated) peptic ulcer disease had a 12 times higher chance of being classified as “high-risk” by the general practitioner compared with patients without a history of (complicated) peptic ulcer disease (OR 12.0, 95% CI 5.51 - 26.1). After adjustment for all variables listed in Table 6, all tested variables were independently associated with risk classification by the general practitioner. In addition, the number of risk factors was found to be independently associated with the general practitioners’ classification as high risk; general practitioners more frequently classified patients adequately if several risk factors were present.

Table 6: Risk factors associated with general practitioner assessment for patients to be at high risk for gastrointestinal complications (average risk served as a reference)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>0.91 (0.70 - 1.18)</td>
<td>0.93 (0.70 - 1.24)</td>
</tr>
<tr>
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<td>0.97 (0.59 - 1.58)</td>
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</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>History of PUD</td>
<td>0.85 (0.60 – 1.21)</td>
<td>0.86 (0.59 – 1.25)</td>
</tr>
</tbody>
</table>


SAFETY

All patients were included in safety analysis. One patient stopped esomeprazole preliminary because of diarrhoea. This patient used meloxicam at inclusion. No serious side-effects were reported.
DISCUSSION

In our study, reflecting current daily practice, we assessed the effect of esomeprazole on NSAID-associated gastrointestinal symptoms in 1042 patients. Response was seen in 81% of patients, and 57% of patients reported a maximum of 1 day per week of upper gastrointestinal symptoms. An additional 24% had a partial response. We found that esomeprazole consistently and significantly decreased the symptom scores for all four studied gastrointestinal symptoms, that is, heartburn, regurgitation, bloating and nausea. The beneficial response was present irrespective of risk for upper gastrointestinal complications. Patients with comorbidity or comedication, or patients on nonselective or COX-2 selective NSAID fared equally well. History of peptic ulcer disease and presence of more than one established risk factor were the strongest predictors for patients to be classified as high risk by the general practitioner. Earlier randomized clinical trials have shown that 20 mg or 40 mg esomeprazole provides relief of upper gastrointestinal symptoms in approximately 70% of patients using nonselective NSAIDs or COX-2 inhibitors. We confirmed these results, but our response rates were slightly lower. This reflects the difference between a randomized clinical trial and daily practice. Patients participating in randomized trials are highly selected, and patients who are commonly seen in primary care (with comorbidities and multiple drug use) are excluded from randomized clinical trials. Other reasons for decreased efficacy are noncompliance, a higher or lower dose than tested, greater disease severity, and drug interactions. As a consequence, treatment effect of a drug may decrease if it is used in daily practice.

The definition of response, “a maximum of 1 day per week with persistent symptoms”, was in line with relief definitions used in a previous randomized trial in NSAID users and in patients with GERD, in which this is a commonly used method to assess treatment response. Our study showed that more than 10% of patients were taking over-the-counter (OTC) NSAIDs. Generally, OTC NSAIDs are sold in lower dosages and carry less gastrointestinal risk compared with prescribed NSAIDs. However, when a patient is taking both prescribed and OTC NSAIDs the risk of gastrointestinal complications increases, and both patients and physicians are often unaware of this risk. We also registered switchers among NSAID use. Interestingly, most patients switched within either nonselective NSAIDs or COX-2 selective inhibitors, whereas we expected more switchers to COX-2 selective inhibitors in high-risk patients. A minority of 14% of all NSAID users used COX-2 selective inhibitors. This reflects the Dutch gastroprotection guideline, which recommends co-prescription of a PPI or misoprostol for NSAID users at risk for complications. Prescription of a COX-2 selective inhibitor should be considered only when there are major concerns about multiple drug use.

The most frequently reported symptom at inclusion was heartburn (93%), despite exclusion of patients with (a history of) GERD. This seems contradictory but is in line with two multicenter studies that also assessed gastrointestinal symptom relief on PPI therapy in NSAID users in a randomized controlled manner. The strengths of our study are the large number of included patients and the daily practice setting. Patients were included without stringent inclusion and exclusion criteria, reflecting daily practice as much as possible. On the basis of its pragmatic design, our study also has some limitations. We did not perform endoscopy before inclusion or at treatment evaluation. In Dutch daily practice, the majority of patients visiting a general practitioner with upper gastrointestinal symptoms are at first pragmatically treated with acid-suppressive drugs without prior endoscopic procedures. This is based on the high rates of ‘functional’ dyspepsia - that is, no organic cause for upper gastrointestinal complaints can be found. Referral for endoscopy is only warranted if alarming symptoms are present or if symptoms persist after adequate treatment with acid suppressors. This fell outside the scope of this study. We did not perform any diagnostic test for Helicobacter pylori infection either. Although many studies have been conducted regarding the association between H. pylori infection and upper gastrointestinal symptoms, the actual contribution of H. pylori in patients with upper gastrointestinal symptoms is still under debate.

Second, we did not include a placebo group. The efficacy of esomeprazole has already been proven: withholding effective treatment from patients is unethical. By using this pragmatic design, we were able to estimate how patients responded to esomeprazole in daily primary care. Third, we cannot rule out selection bias in our cohort of Dutch patients visiting their general practitioner for upper gastrointestinal symptoms while on NSAID therapy. Not all patients with NSAID-associated upper gastrointestinal symptoms will decide to visit a general practitioner for their upper gastrointestinal symptoms; moreover, we were dependent on general practitioners who selected NSAID users for participation in the study. We believe that the resemblance of daily practice and the large number of patients included in our study outweigh these shortcomings.

In conclusion, PPIs are effective in diminishing upper gastrointestinal symptoms in NSAID users in daily general practice. The type of NSAID and patients’ gastrointestinal risk according to the general practitioner did not seem to affect esomeprazole’s effectiveness.
Chapter 7

REFERENCES


Chapter 8

Gastrointestinal symptoms in low-dose aspirin users in the community:
a comparison between plain aspirin and effervescent calcium carbasalate

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Marc A Brouwer
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Martijn GH van Oijen

Submitted
INTRODUCTION

Optimal antithrombotic therapy has proven to be essential in secondary prevention in cardiovascular disease. In this, aspirin (acetylsalicylic acid) has a pivotal role and is associated with a relative reduction of approximately 25% on recurrent cardiovascular events. However, gastric toxicity is a well-known side effect of aspirin presenting as gastric or duodenal ulcers, bleeding and dyspepsia. Of these, dyspepsia is mostly reported which is present in 20-40% of chronic aspirin users and is associated with reduced compliance, increased healthcare costs and reduced health-related quality of life. To reduce gastrointestinal damage different formulations of aspirin have been developed. These formulations either inhibit the release of aspirin in the stomach (enteric-coated aspirin), facilitate the transit of aspirin across the gastric mucous layer (the newly developed PL2200), or increase solubility of aspirin supposedly resulting in lower local concentrations (effervescent calcium carbasalate (ECC)). All these forms were mainly studied in high dosages and showed clear benefit with respect to gastric ulcer formation when studied in healthy volunteers. However, when investigating its clinical effect in patients on (low-dose) chronic antiplatelet therapy, no clear beneficial effect on gastrointestinal side effects was noticeable.

Data on the effects of the various aspirin formulations on gastrointestinal symptoms are scarce. With respect to enteric-coated aspirin, the currently available literature does not indicate that this would reduce gastrointestinal complaints when compared to plain aspirin. In the Netherlands, a total of 1,290,000 patients were using low-dose aspirin of which 41% used ECC. In contrast to enteric-coated aspirin, no data are published comparing the effects of ECC and plain aspirin on gastrointestinal symptoms. We hypothesize that in our population-based cohort of respondents using low-dose aspirin, the prevalence of gastrointestinal symptoms is lower in those using effervescent calcium carbasalate compared to plain aspirin. We also anticipate that respondents using different formulations may present with different type of gastrointestinal symptoms.

METHODS

STUDY POPULATION

We sent 51,869 questionnaires by surface mail to a representative sample of the Dutch population in December 2008. Invited subjects were aged 18 years and above, and randomly selected from municipal databases of five different municipalities selected on their geographical location in the Netherlands, in order to gather a representative sample.
of the Dutch population. We included returned questionnaires until March 31st 2009. We excluded returned questionnaires with missing elements that were part of the primary outcome measure. We also excluded returned questionnaires in which all baseline characteristics were missing or when the medication was unreadable or if the used aspirin formulation was not reported. The complete cohort was described previously.\textsuperscript{24} The current sample size consisted of those respondents reporting the use of either low dose plain aspirin or effervescent calcium carbasalate.

The Medical Ethical Committee of the Radboud University Nijmegen assessed the research proposal of this study and concluded that it could be waived for ethical review, as questionnaires were returned and stored anonymously, and (non-)responders would not be contacted again. For this reason, we did not obtain written informed consent.

QUESTIONNAIRE

The questionnaire has been used before and was specifically designed for collection of demographic information, gastrointestinal symptoms, and medication use.\textsuperscript{25,26} Participants were asked whether they suffer from gastrointestinal symptoms in general and about the presence of 26 gastrointestinal symptoms such as nausea, early satiety and bloating. Severity of gastrointestinal symptoms was assessed on a seven-point Likert scale (0 = absent, 1 = almost absent, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe) over the preceding four weeks.\textsuperscript{27} A symptom was considered to be present if the participants scored ≥ 2 on the Likert scale.

OUTCOMES

Our primary outcome was the presence of gastrointestinal symptoms, which was assessed with the question: “Do you experience gastrointestinal complaints?” and had to be answered with either “yes” or “no”. Secondary outcomes were duration of the primary endpoint and the individual gastrointestinal symptoms among responders who reported the presence of gastrointestinal complaints. The primary and secondary outcomes were compared between respondents reporting the use of low-dose plain aspirin (80mg) and those using effervescent calcium carbasalate (100mg).

STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS statistical software, version 16.0 (SPSS, Inc., Chicago, Illinois, USA). Frequency tables were provided describing respondents’ baseline characteristics. Pearson’s chi-square ($\chi^2$) test was used to compare categorical variables. Continuous variables were compared with the Student’s t-test or the Mann-Whitney U method whenever appropriate. Univariate and multivariate associations for gastrointestinal endpoints in respondents using plain aspirin or ECC were analyzed using logistic regression. A p-value of < 0.05 was considered statistically significant.

Covariates were included in multivariate analysis if they significantly differed between respondents using effervescent calcium carbasalate versus plain aspirin. In addition were those covariates associated with gastrointestinal symptoms at a level of p < 0.1 in the univariate analysis included in the multivariate analysis. Using forward selection, a covariate was allowed into the multivariate model if it influenced the model with a likelihood ratio significance level of p < 0.05, and was removed again if its significance level exceeded p = 0.1 during any of the following steps. The type of formulation used (effervescent calcium carbasalate versus plain aspirin) was forced into the model.

RESULTS

A total of 18,317 (35%) questionnaires were returned, of which 742 unopened for various reasons (Figure 1).
participants using plain aspirin, those with ECC were older, reported more comorbidity and were using more co-medication (Table 1).

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Medication use (%)</th>
<th>Plain aspirin n = 911</th>
<th>Effervescent calcium carbasalate n = 633</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>494 (56)</td>
<td>377 (61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>160 (18)</td>
<td>116 (19)</td>
<td>0.74</td>
</tr>
<tr>
<td>Body mass index (sSD) (kg/m²)</td>
<td>26.3 (4.6)</td>
<td>27.0 (4.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>108 (12)</td>
<td>106 (17)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>53 (6)</td>
<td>54 (9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>62 (7)</td>
<td>69 (11)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>16 (2)</td>
<td>9 (1)</td>
<td>0.61</td>
</tr>
<tr>
<td>IBD</td>
<td>27 (3)</td>
<td>18 (3)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

The self-reported prevalence of gastrointestinal symptoms of plain aspirin and ECC were 26.3%, and 27.5%, respectively. When comparing self-reported gastrointestinal symptoms between plain aspirin and ECC we observed no difference (ECC: OR 1.06, 95% CI 0.84 - 1.33). Also after adjustment with multivariate regression for multiple possible confounders there was no significant difference between plain aspirin and ECC for the presence of gastrointestinal symptoms (ECC: aOR 1.08, 95% CI 0.83 - 1.41, Table 2). Among those reporting gastrointestinal symptoms, respondents using ECC had a significantly longer history of symptoms (10 years, IQR 4 - 20) compared to participants using plain aspirin (7 years, IQR 3 - 16, p = 0.04).

Table 2: Multivariate logistic regression model for reporting gastrointestinal symptoms with effervescent calcium carbasalate entered into the model

<table>
<thead>
<tr>
<th>Medication use (%)</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>0.71</td>
<td>0.50 - 0.92</td>
<td>0.01</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.54</td>
<td>1.01 - 2.36</td>
<td>0.046</td>
</tr>
<tr>
<td>IBD</td>
<td>2.01</td>
<td>1.00 - 4.04</td>
<td>0.050</td>
</tr>
<tr>
<td>Medication use (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td>3.96</td>
<td>2.96 - 5.30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>H2RA</td>
<td>4.39</td>
<td>2.01 - 9.57</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Antacids</td>
<td>2.90</td>
<td>1.90 - 4.44</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.42</td>
<td>1.09 - 1.86</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Effervescent calcium carbasalate</td>
<td>1.08</td>
<td>0.83 - 1.41</td>
<td>0.57</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>2.39</td>
<td>1.60 - 3.58</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease, H2RA: H2-receptor antagonist, IBD: inflammatory bowel disease, PPI: proton pump inhibitor

In respondents reporting the presence of gastrointestinal symptoms and using either plain aspirin or ECC, the most frequently reported upper gastrointestinal symptoms were bloating (61%), belching (47%) and regurgitation (42%; Figure 2a). Flatulence (70%) and borborygmi (56%) were the most frequently reported lower gastrointestinal symptoms (Figure 2b). No significant differences between plain aspirin and ECC were present for any of the gastrointestinal symptoms.
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Gastrointestinal symptoms in low-dose aspirin users

DISCUSSION

We aimed to compare the prevalence of self-reported gastrointestinal symptoms between respondents using plain aspirin and those who were prescribed ECC. We observed that in respondents using any form of low-dose aspirin the prevalence of gastrointestinal symptoms was 27%. The use of ECC is not associated with less gastrointestinal symptoms compared to plain aspirin. Most reported upper gastrointestinal symptoms were bloating, belching, and regurgitation, whereas flatulence and borborygmi were reported most for lower gastrointestinal symptoms. No differences in type of symptoms between users of ECC and plain aspirin were observed.

The prevalence of gastrointestinal symptoms in our study cohort is in line with previously reported data of aspirin users. Interestingly, the prevalence is also comparable with the general (mostly non-aspirin using) population. The selection of our study population could have contributed to this finding. Low-dose aspirin is generally a long-term treatment, i.e. for the remainder of the patients’ life span. For our study we selected all low-dose aspirin users from a large cohort of participants returning the questionnaire. As a result of our design the odds that aspirin treatment was recently initiated for our participants are minimal. Those patients who suffered from gastrointestinal symptoms during (the initiation of) aspirin treatment were likely to receive co-treatment with a PPI, H2 receptor antagonist or antacid or were even switched to other antiplatelet agents. Consequently, our cohort consists of a selected population of respondents in whom aspirin is relatively well tolerated. This hypothesis is supported by more frequently use of gastroprotective agents in low-dose aspirin users compared to the general population (e.g. PPI use: 24.5% vs 10.6%). Irrespective, our data indicates that ECC is of no beneficial value for gastrointestinal symptoms among our population of long-term aspirin users.

So far, only two studies have been conducted to investigate endoscopically proven gastric mucosal damage in users of ECC and plain aspirin. In a randomized cross-over trial, ECC significantly reduced endoscopically observed gastric erosions and ulcers compared to the bioequivalent dose of plain aspirin. However, this study assessed healthy volunteers, investigated very high doses of aspirin (650mg t.i.d.) and only studied the short-term effects. More recently, the effects of low-dose ECC and plain aspirin were compared in patients using long-term aspirin for cardiovascular prevention. In this large retrospective cohort study, the authors concluded that the incidence rates of endoscopically proven peptic ulcers were not significantly different between both groups.

Figure 2: Type and prevalence of specific upper (a) and lower (b) gastrointestinal symptoms in respondents experiencing gastrointestinal symptoms categorized by aspirin formulation
ECC: effervescent calcium carbasa late
In view of our finding that ECC is not associated with a reduction in gastrointestinal symptoms and taken into account the higher costs of ECC compared to plain aspirin, we feel that plain aspirin is the first drug of choice. If gastrointestinal symptoms occur, we advise to prescribe a relatively cheap PPI or another gastroprotective agent, albeit that this is only of limited value.29-30 Only if this does not reduce the symptoms, one might consider ECC as an alternative to plain aspirin.

In conclusion, the prevalence of gastrointestinal symptoms among aspirin users in the Dutch community is 27% with no difference between effervescent calcium carbamate and plain aspirin in overall prevalence and type of symptoms reported.
Chapter 8


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Chapter 9

Antidepressants and gastrointestinal symptoms in the general Dutch adult population

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INTRODUCTION

Antidepressants are frequently prescribed medications. Its use has risen tremendously over the last decades, which is associated with high healthcare expenditures.\(^1\-^3\) In 2011, 264 million prescriptions for antidepressants were made in the United States, with associated costs of 11 billion dollar, which is equivalent to approximately 8 billion Euros.\(^4\) In the Netherlands, antidepressant use accounted for 47 million Euros in 2011.\(^5\)

In well-designed clinical trials that assessed the effectiveness of antidepressants for psychiatric disorders, gastrointestinal symptoms were frequently reported adverse effects.\(^6\-^10\)

A meta-analysis that assessed side effects of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) confirmed these findings.\(^11\)

Years later, the effect of antidepressants was studied in patients with functional digestive disorders.\(^12\)-\(^14\) A number of randomized clinical trials investigated the efficacy of antidepressant treatment in improving gastrointestinal symptoms in patients with irritable bowel syndrome (IBS) and functional dyspepsia.\(^13,15,16\) Subsequent systematic reviews concluded that antidepressants have beneficial effects in these patients.\(^17\)-\(^19\) Although one review signalled possible publication bias\(^17\), clinical guidelines incorporated antidepressants as second line treatment option for functional gastrointestinal disorders.\(^20\)

Given the ambiguous effect of antidepressants on the gastrointestinal system we set out to assess the association between use of antidepressants and gastrointestinal symptoms in the general population.

STUDY POPULATION

We sent 51,869 questionnaires to a random sample of the adult Dutch population in December 2008. Invited subjects were eighteen years and older, and were randomly selected from municipal databases of five different Dutch municipalities. The municipalities were selected to achieve a representative sample of the population. Questionnaires that returned until the end of March 2009 were included in the study. Questionnaires were excluded if 1) baseline variables were missing, 2) the primary outcome was missing, 3) type of symptoms was missing, and/or 4) illegible input of medication.

ASSESSMENT INSTRUMENT

We used a questionnaire that was used previously and that was specifically designed to collect information on gastrointestinal symptoms, medication use, comorbidity, and health-related quality of life.\(^21\)-\(^23\)
Respondents were asked about the general presence of gastrointestinal symptoms. We also questioned the following 16 different symptoms: epigastric pain (in general, during daytime, nocturnal), heartburn (in general, during daytime, nocturnal), regurgitation, borborygmi, bloating, empty feeling, nausea, vomiting, loss of appetite, early satiety, belching, haematemesis, dysphagia (for liquids, for solid food), lower abdominal pain (in general, postprandial, pre-prandial, persistent after defecation), flatulence, and abnormal stools (black, bloody, mucous, frequently hard, diarrhoea, alternately solid or loose, constipation, painful defecation, strong urgency, incomplete, fatty stools). Respondents could indicate severity of symptoms over the preceding four weeks on a seven-point Likert scale (0 = absent, 1 = almost absent, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe). A symptom was considered present if respondents rated it ≥ 2 on the Likert scale.

We asked for medication use and categorized antidepressants into: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and a group of “other antidepressants” (tetracyclic antidepressants, monoamine oxidase (MAO) inhibitors, and type of antidepressants not specified). Respondents were categorised as antidepressant users and non-antidepressant users (‘non-users’).

Consumption of ≥ 42 units coffee per week was defined as excessive coffee consumption. Body mass index (BMI) was calculated and categorised into normal weight (BMI < 25 kg/m²) and overweight (BMI ≥ 25 kg/m²).

Presence of depressive symptoms was scored with the EuroQol 5D.25 We classified respondents that indicated to be ‘moderately anxious/depressed’ or ‘extremely anxious/depressed’ as having depressive symptoms.

OUTCOMES

Our primary outcome was presence of gastrointestinal symptoms, which was assessed with the question: “Do you experience gastrointestinal complaints?” and had to be answered with either “yes” or “no”. Type of gastrointestinal symptoms was the secondary outcome measure.

DATA ANALYSIS

Data from the questionnaires were entered into a database using Teleform automated scanning software, and statistical analyses were performed with IBM PAWS Statistics SPSS, version 18.0. Presence of gastrointestinal symptoms in antidepressant users and non-antidepressant users was analyzed with a Pearson’s chi-square (\( \chi^2 \)) test. In respondents with gastrointestinal symptoms, type of symptoms was compared between antidepressant users and non-users with Pearson’s chi-square (\( \chi^2 \)) test. Continuous variables were compared with Student’s t-test or Mann-Whitney U method whenever appropriate.

Univariable logistic regression analysis was performed to determine which variables were associated with the primary outcome. Variables were included in the multivariable regression analysis if a significant association with gastrointestinal symptoms was found (p < 0.01) and/or if a biological plausibility for an association between antidepressant use and gastrointestinal symptoms was present. We included the following variables in the multivariable regression analysis: demographic factors (age and gender), lifestyle factors (overweight, smoking, and excessive coffee consumption), comorbidity (rheumatoid arthritis, asthma/COPD, IBS, and depressive symptoms), history of peptic ulcer disease and peptic ulcer bleeding, and medication use.

Subgroup analyses were conducted to assess presence of gastrointestinal symptoms in the subgroups of respondents with and without IBS using regression analysis. Use of antidepressants in these groups was assessed using Pearson’s chi-square (\( \chi^2 \)) test. Class of antidepressant and its association with gastrointestinal symptoms was calculated using univariable and multivariable regression analysis.

Due to the large number of respondents, a p-value < 0.01 was the cut-off point for statistical significance. Odds ratios were presented with 95% confidence intervals (CI).

RESULTS

We received a total of 18,317 questionnaires (response rate 35.3%), and 742 (4.1%) were returned to sender for various reasons (Figure 1). Of the remaining questionnaires (n = 17,575), an additional 817 questionnaires (4.6%) were excluded based on predefined exclusion criteria, leaving 16,758 questionnaires eligible for analyses. Mean age of respondents was 49.8 years (SD 15.7) and 43% was male.

Antidepressant use was reported by 701 respondents (4.2%), of which 60% used SSRIs (n = 423), 19% TCAs (n = 133), 13% SNRIs (n = 89), and 8% reported use of another antidepressant (n = 56). Table 1 depicts the baseline characteristics of the included population categorised by antidepressant use. Antidepressant users were older, more often female, and reported more frequently additional medication use such as proton pump inhibitors (PPIs), nonsteroidal anti-inflammatory drugs (NSAIDs) and anxiolytics.

Gastrointestinal symptoms were more frequently among antidepressant users compared to non-users (40% vs. 25%, p < 0.01) with an unadjusted odds ratio (OR) of 1.96 (95% CI 1.68 - 2.29). Amongst others, antidepressant users more frequently reported: flatulence (78% vs. 70%), bloating (71% vs. 63%), and epigastric pain during daytime (54% vs. 39%) compared to non-users (all p < 0.01). Symptoms that were more common in antidepressant users are depicted in Figures 2A and 2B.

A total of 18% of the examined population (n = 2,894) reported depressive symptoms. Antidepressant users more frequently reported depressive symptoms compared to
We performed several predefined subgroup analyses.

After multivariable regression analysis, the difference in gastrointestinal symptoms between antidepressant users and non-users was not statistically significant (adjusted OR 0.94, 95% CI 0.74 - 1.18). We found that use of PPIs, H₂ receptor antagonists (H₂RAs), laxatives, and presence of IBS was strongly associated with gastrointestinal symptoms (Table 3). After adjusting for confounders, this was no longer significant (adjusted OR 0.74 - 1.18). We found that use of PPIs increased among respondents who reported depressive symptoms (46% vs. 22%, p < 0.01). Presence of gastrointestinal symptoms was increased among respondents who reported depressive symptoms (46% vs. 22%, p < 0.01). Depressive symptoms were more prevalent in respondents with gastrointestinal symptoms (36% vs. 17%, p < 0.01).

**Table 1: Baseline characteristics of antidepressant and non-antidepressant users**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Antidepressant users</th>
<th>Non-antidepressant users</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (± SD)</td>
<td>52.9 (13.6)</td>
<td>49.7 (15.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Female gender (%)</td>
<td>485 (71.1)</td>
<td>8,747 (56.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Body mass index ≥ 25 kg/m² (%)</td>
<td>388 (56.6)</td>
<td>7,228 (45.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>210 (30.5)</td>
<td>2,719 (17.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Excessive coffee consumption (%)</td>
<td>78 (12.8)</td>
<td>1,515 (11.0)</td>
<td>0.162</td>
</tr>
<tr>
<td>Medication use (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td>162 (23.1)</td>
<td>1,609 (10.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>H₂RAs</td>
<td>32 (4.6)</td>
<td>255 (1.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Antacids</td>
<td>71 (10.1)</td>
<td>954 (5.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>186 (26.5)</td>
<td>3,047 (19.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>207 (29.5)</td>
<td>3,974 (24.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Anxiolytic agents</td>
<td>100 (14.3)</td>
<td>252 (1.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Antipsychotic agents</td>
<td>45 (6.4)</td>
<td>61 (0.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Laxatives</td>
<td>39 (5.6)</td>
<td>235 (1.5)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>$\beta$-sympathomimetics</td>
<td>58 (8.3)</td>
<td>657 (4.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Anti-migraine medications</td>
<td>15 (2.1)</td>
<td>171 (1.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Parasympathomimetis</td>
<td>19 (2.7)</td>
<td>192 (1.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sleep medications</td>
<td>60 (8.6)</td>
<td>191 (1.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Comorbidity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported depressive symptoms</td>
<td>282 (55.5)</td>
<td>2,512 (16.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>74 (10.6)</td>
<td>699 (4.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>75 (10.7)</td>
<td>969 (6.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>84 (12.0)</td>
<td>811 (5.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>History (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>52 (7.6)</td>
<td>834 (5.3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Peptic ulcer bleeding</td>
<td>14 (2.0)</td>
<td>268 (1.7)</td>
<td>0.491</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease, H₂RA: H₂-receptor antagonist, NSAID: nonsteroidal anti-inflammatory drug, PPI: proton pump inhibitor

*Excessive coffee consumption: 42 cups a week and more

**Table 3**

17,575 completed questionnaires received

- 51,869 questionnaires sent
- 18,317 questionnaires returned (response rate 35.3%)
- 742 questionnaires returned to sender (360 no reason, 298 moved, 47 deceased, 37 not interested)
- 587 questionnaires excluded (284 all baseline variables missing, 385 primary outcome missing, 413 gastrointestinal symptoms missing, 111 medication unreadable)
- 16,758 questionnaires analysed

51,869 questionnaires sent

18,317 questionnaires returned (response rate 35.3%)

742 questionnaires returned to sender

587 questionnaires excluded

16,758 questionnaires analysed

701 (4.2%) Antidepressant users

16,057 (85.8%) Other respondents

* Some respondents fulfilled more than 1 exclusion criterion
Chapter 9

Antidepressants and gastrointestinal symptoms

Figure 2A: Upper gastrointestinal symptoms reported significantly more frequently by antidepressant users compared to other respondents

Figure 2B: Lower gastrointestinal symptoms reported significantly more frequently by antidepressant users compared to other respondents

Table 2: Unadjusted and adjusted odds ratio for presence of gastrointestinal symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant use</td>
<td>1.96 (1.68 – 2.29)</td>
<td>0.94 (0.74 – 1.18)</td>
</tr>
<tr>
<td>Age (per advancing year)</td>
<td>1.00 (0.99 – 1.00)</td>
<td>0.98 (0.98 – 0.98)</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.70 (1.58 – 1.83)</td>
<td>1.52 (1.38 – 1.67)</td>
</tr>
<tr>
<td>Body mass index ≥ 25 kg/m²</td>
<td>1.15 (1.07 – 1.23)</td>
<td>1.07 (0.97 – 1.18)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.20 (1.10 – 1.31)</td>
<td>1.04 (0.92 – 1.17)</td>
</tr>
<tr>
<td>Excessive coffee consumption a</td>
<td>0.83 (0.74 – 0.95)</td>
<td>1.01 (0.87 – 1.18)</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td>7.14 (6.43 – 7.94)</td>
<td>7.80 (6.76 – 9.01)</td>
</tr>
<tr>
<td>H2RAs</td>
<td>8.52 (6.53 – 11.1)</td>
<td>9.12 (6.48 – 12.8)</td>
</tr>
<tr>
<td>Antacids</td>
<td>4.33 (3.81 – 4.93)</td>
<td>4.30 (3.63 – 5.08)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>1.58 (1.46 – 1.72)</td>
<td>0.96 (0.85 – 1.08)</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1.29 (1.20 – 1.40)</td>
<td>1.04 (0.94 – 1.16)</td>
</tr>
<tr>
<td>Anxiolytic agents</td>
<td>3.03 (2.46 – 3.75)</td>
<td>1.54 (1.12 – 2.11)</td>
</tr>
<tr>
<td>Antipsychotic agents</td>
<td>1.62 (1.09 – 2.41)</td>
<td>0.63 (0.36 – 1.13)</td>
</tr>
<tr>
<td>Laxatives</td>
<td>6.43 (4.96 – 8.32)</td>
<td>4.82 (3.27 – 7.09)</td>
</tr>
<tr>
<td>β2-sympathicomimetics</td>
<td>1.61 (1.37 – 1.88)</td>
<td>0.67 (0.50 – 0.90)</td>
</tr>
<tr>
<td>Anti-migraine medications</td>
<td>1.60 (1.18 – 2.16)</td>
<td>1.24 (0.82 – 1.89)</td>
</tr>
<tr>
<td>Parasympathicomimetics</td>
<td>1.67 (1.26 – 2.21)</td>
<td>1.13 (0.74 – 1.72)</td>
</tr>
<tr>
<td>Sleep medications b</td>
<td>2.52 (1.96 – 3.24)</td>
<td>1.62 (1.13 – 2.32)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reported depressive symptoms</td>
<td>3.07 (2.82 – 3.34)</td>
<td>2.35 (2.09 – 2.63)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>2.07 (1.79 – 2.40)</td>
<td>1.06 (0.85 – 1.31)</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.82 (1.59 – 2.07)</td>
<td>1.47 (1.15 – 1.88)</td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td>10.8 (9.26 – 12.7)</td>
<td>9.98 (8.12 – 12.28)</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>4.02 (3.50 – 4.61)</td>
<td>2.25 (1.85 – 2.74)</td>
</tr>
<tr>
<td>Peptic ulcer bleeding</td>
<td>3.73 (2.94 – 4.73)</td>
<td>1.80 (1.29 – 2.52)</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease, H2RA: H2-receptor antagonist, NSAID: nonsteroidal anti-inflammatory drug, PPI: proton pump inhibitor

aExcessive coffee consumption: 42 cups a week and more

bBrotizolam, flunitrazepam, flurazepam, loprazolam, lormetazepam, melatonin, midazolam, nitrazepam, temazepam, zopiclon, non specified sleep medications
Table 3: Unadjusted and adjusted odds ratios for presence of gastrointestinal symptoms in antidepressant subgroups

<table>
<thead>
<tr>
<th>Class of antidepressant</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>1.57 (1.10 – 2.25)</td>
<td>0.60 (0.35 – 1.04)</td>
</tr>
<tr>
<td>SSRI s</td>
<td>1.90 (1.56 – 2.32)</td>
<td>0.91 (0.68 – 1.21)</td>
</tr>
<tr>
<td>SNRIs</td>
<td>2.54 (1.67 – 3.86)</td>
<td>1.24 (0.67 – 2.30)</td>
</tr>
<tr>
<td>Other antidepressantsa</td>
<td>2.58 (1.52 – 4.37)</td>
<td>1.63 (0.75 – 3.56)</td>
</tr>
</tbody>
</table>

SNRI: serotonin and norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressants

aTetracylic antidepressants, MAO inhibitors, and class of antidepressants not specified

DISCUSSION

In our large general population-based study, antidepressant users more frequently reported gastrointestinal symptoms. However, after adjustment for potential confounders, there remained no association between antidepressant use and gastrointestinal symptoms.

No previous studies have assessed the association between antidepressant use and gastrointestinal symptoms in the general population. However, depression and gastrointestinal symptoms were studied before: a survey from the general population assessed frequency of gastrointestinal symptoms in respondents with and without depressive symptoms, and found that 54% of respondents with depression frequently reported abdominal pain, diarrhea, constipation, dyspepsia, or IBS compared to 29% of non-depressed controls. Unfortunately, this study did not assess antidepressant use in relation to gastrointestinal and depressive symptoms, but noted the frequent co-occurrence of depression and somatic complaints.

We found that depressive symptoms are an important confounder in the association between antidepressant use and gastrointestinal symptoms. In our study, respondents with depressive symptoms had a 24% increased risk for presence of gastrointestinal symptoms. This is in line with other studies in the field. An ongoing study that compares the effectiveness of SSRI s, TCAs, and placebo in patients with functional gastrointestinal disorders (with or without concomitant depression) will hopefully add knowledge to the understanding of the complex interplay between depression and functional gastrointestinal symptoms.

Our study has a number of strengths and limitations. First, we studied the presence of gastrointestinal symptoms in antidepressant users in a largely randomly selected sample of the general population. Most other similar studies included patients from primary, secondary, and/or tertiary care centres that had strict inclusion criteria. Second, we were able to adjust for confounders using multivariable analysis with many covariates. This supported the assumption that the univariable association between antidepressant use and gastrointestinal symptoms is attributable to bias.

In our study the possibility of selection bias cannot be excluded. We tried to minimize this by sending a personalized invitation letter and ask all invitees to complete the questionnaire, irrespective of the presence of gastrointestinal symptoms. Of all respondents returning the questionnaire, 26% experienced gastrointestinal symptoms, which is similar to another study that assessed prevalence of upper gastrointestinal symptoms in the Netherlands. This supported the assumption that the univariable association between antidepressant use and gastrointestinal symptoms was attributable to bias. This suggests that presence of selection bias in our study might be limited. Due to our study design we were unable to send reminders or to perform non-responder research. Another limitation is that we do not have detailed information about antidepressant dose and duration of use. Lower dosages of SSRI s seem to be associated with fewer side effects, while the association between dosages of TCAs and adverse effects is ambiguous. The lack of information on duration of antidepressant therapy may have confounded the association between antidepressant use and gastrointestinal symptoms, because adverse effects may predominate the first weeks of therapy. We assume that the majority of antidepressant users are long-term users, as was shown by Moore et al.

The results of our study have clear implications for clinical practice. As known, patients using antidepressants are at risk of developing gastrointestinal symptoms, because these symptoms are frequently reported adverse effects. These side effects develop shortly after initiation of therapy, and usually precede the desired clinical effect by several weeks. This profile is inherent to this class of drugs and should be discussed with the patient prior to the start of antidepressant treatment. Another implication is that the evaluation of this class of drugs should include assessment of psychiatric but also gastrointestinal symptoms. In case a depressive patient develops gastrointestinal symptoms during therapy, emphasis should be put on adequate treatment of depression rather than alleviating the gastrointestinal symptoms. In practice this may result in increasing the dosage of antidepressants rather than tapering. For a treating physician this is a rather counterintuitive approach. In conclusion, we found that antidepressant users more frequently reported presence of gastrointestinal symptoms than non-users. However, after adjusting for confounders, no association between antidepressant use and gastrointestinal symptoms was observed.
REFERENCES


Gastrointestinal symptoms are very common and the majority of upper gastrointestinal symptoms in the community can be broadly classified as functional dyspepsia. The current thinking is that the causes and contributing factors for functional dyspepsia are manifold. Similarly, there is no universal treatment for functional dyspepsia. At the individual level, gastrointestinal symptoms greatly impact health-related quality of life and at macro-economical level, these symptoms have profound implications for our healthcare system.\textsuperscript{1-4} In this thesis we studied the current prevalence of gastrointestinal symptoms in a random sample of the population. We assessed which factors are associated with presence of gastrointestinal symptoms with a focus on medication use. In addition to assess the mere presence of gastrointestinal symptoms, we also addressed health-related quality of life as an outcome measure. We are aware that multiple studies focusing on presence of gastrointestinal symptoms have been performed in the past. However, the prevalence of risk factors for gastrointestinal symptoms, such as Helicobacter pylori and use of gastrotoxic medication, has changed considerably. This calls for a critical reassessment of the older data in view of the changed environment.\textsuperscript{5,7}

ANSWERS TO QUESTIONS ADDRESSED IN THIS THESIS

1. What is the current prevalence of gastrointestinal symptoms in the Dutch general population?

We studied this question by sending a questionnaire to more than 50,000 randomly selected Dutch adult inhabitants. We found that the current prevalence of gastrointestinal symptoms was 26%. We found that females more frequently reported gastrointestinal symptoms, which is in line with other similar studies.\textsuperscript{8-10} In our study, presence of asthma or COPD was independently associated with gastrointestinal symptoms. Asthma is associated with GERD, although the exact mechanism remains to be elucidated.\textsuperscript{11,12} Recent studies in patients with COPD also report an increased prevalence of GERD symptoms.\textsuperscript{15-16} Medication use, and especially paracetamol, antidepressants, and acid-suppressive medication contributed significantly to presence of gastrointestinal symptoms in our large population-based survey. The independent association detected for paracetamol probably stems from the use of paracetamol as a panacea for gastrointestinal symptoms. We surmise that this hypothesis also applies to the relation between acid-suppressive medication and gastrointestinal symptoms. The association between antidepressants and gastrointestinal symptoms is complex due to the interactions between: 1) depression and gastrointestinal symptoms, 2) depression and antidepressant use, and 3) antidepressant use and gastrointestinal symptoms.\textsuperscript{16-24} In this thesis we found that the association between gastrointestinal symptoms and antidepressant use was not statistically significant after correction for multiple confounders.

Plain low-dose aspirin and carbasalate calcium are frequently used in the Netherlands for the secondary prevention of cardiovascular events. Based on studies in healthy volunteers and following pharmacological principals, it is thought that carbasalate calcium possesses a safer gastrointestinal profile. We, however, were not able to confirm this hypothesis in clinical practice.

2. What is the consequence of gastrointestinal symptom presence on health-related quality of life?

In addition to prevalence of gastrointestinal symptoms, we also studied health-related quality of life. In our general population survey we assessed health-related quality of life using the EuroQol EQ-5D.\textsuperscript{25} We found that the reported health-related quality of life in respondents with gastrointestinal symptoms was significantly lower compared with those without these symptoms. We did not use a disease-specific quality of life questionnaire. These questionnaires focus on specific disease entities, such as dyspepsia, gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS) etcetera.\textsuperscript{26-30} The disadvantage is that these questionnaires are highly disease focused and less sensitive to detect general gastrointestinal symptoms. For the aim of thesis, which was to assess gastrointestinal symptoms in general, these disease-specific questionnaires were not suitable. We also assessed health-related quality of life in our Internet survey of respondents with GERD. Health-related quality of life was significantly decreased in respondents with more gastrointestinal symptoms.

3. What is the role of NSAIDs on gastrointestinal symptoms and complications?

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause a large variety of gastrointestinal events, from dyspepsia to life-threatening bleeding. We found that NSAID users more frequently reported gastrointestinal symptom presence compared with respondents that did not use NSAIDs. Users of prescribed NSAIDs more frequently reported gastrointestinal symptoms compared with over-the-counter (OTC) NSAID users, but this difference disappeared after statistical correction with multivariable regression analysis. This implicates that NSAID use, irrespective of used dose, is a determinant for gastrointestinal symptoms.

4. What is the role of PPIs in the treatment of gastrointestinal symptoms?

We demonstrated that proton pump inhibitor (PPI) use relieves NSAID-associated gastrointestinal symptoms. We also found through our (large paper-based) questionnaire study that PPI use was independently associated with presence of gastrointestinal symptoms. We assume this is caused by the cross-sectional design that does not allow us to detect and establish causal links. Previous studies demonstrated that PPIs and...


H₂-receptor antagonists (H₂RAs) have a better efficacy than antacids and placebo in the treatment of functional dyspepsia.31-34 It is currently a matter of debate whether the efficacy of PPIs in functional dyspepsia could be explained by the existence of overlap syndromes with GERD.35,36 A Dutch primary care study that assessed cost-effectiveness of different strategies in the treatment of dyspepsia, concluded that starting with an antacid was cost-effective.37 However, since the patent of PPIs has expired, the argument of cost-effectiveness no longer holds. The newest version of the Dutch guideline “dyspepsia” still recommends starting pharmacologic treatment of patients with upper gastrointestinal symptoms with antacids. Reasons for this recommendation are the equal efficacy of antacids and PPIs, the rebound gastric acid hypersecretion after PPI withdrawal, and the drawbacks of long-term PPI use, as increased risk for pneumonia and hip fractures.38-42 However, in clinical practice, many patients visiting a general practitioner with upper gastrointestinal symptoms, frequently have already taken OTC antacids and H₂RAs prior to consultation.

In addition, PPIs are also frequently prescribed in GERD. In our cohort of individuals with GERD that we followed via the internet, we found that two-thirds of those without PPI use reported symptom improvement. This is a very interesting observation, because this supports reserve with PPI prescription if a patient presents with symptoms of GERD for the first time. It would be interesting to examine this population into detail. Did they change their dietary habits; did they lose weight, etcetera? This would be fertile ground for an interesting future study.

**IMPLICATIONS**

Based on the findings of this thesis, we conclude that gastrointestinal symptoms are still very common and negatively impact health-related quality of life. Other studies demonstrated a decreased work efficacy, and high healthcare costs due to these symptoms.1,2 This suggests that strategies focused on improvement of gastrointestinal symptoms may be worthwhile.

Based on these results, we recommend changes in the current Dutch guideline for upper gastrointestinal symptoms. PPI should be the first recommended pharmacological intervention when lifestyle modifications are insufficient in patients with upper gastrointestinal symptoms. This recommendation follows the current daily practice.

Our data are in line with the Dutch guideline “dyspepsia” that NSAID users at advanced age, with a history of peptic ulcer disease, or with concomitant use of low-dose aspirin, anticoagulants of systemic corticosteroids should adhere to a gastroprotective strategy.42 However, we do not agree with the weight assigned to the risk factors that we will discuss below. Presence of severe rheumatoid arthritis, severe diabetes mellitus or severe heart failure is seen as a bona fide indication for gastroprotection but we disagree. Concomitant use of venlafaxine, duloxetine, trazodone or spironolactone also qualifies for gastroprotective strategy and we think that this is unwarranted. The evidence that these risk factors affect ‘general’ NSAID users is scant, and only further complicates the adherence of this guideline by individual physicians.

We do not recommend PPI co-prescription in all NSAID users but favour a targeted strategy and offer PPI to those at risk. Although PPIs are generally safe, they can have serious side effects.40-42 Another argument against a policy that favours PPI co-prescription in all NSAID users is that this strategy promotes polypharmacy, which negatively affects compliance. Therefore, we advise the concomitant prescription of a PPI only in NSAID users at increased risk for gastrointestinal complications.

We favour the use of a structured GERD questionnaire for symptom assessment. A structured questionnaire can support the assessment of symptom severity, in addition to history taking.

**FUTURE PERSPECTIVES**

Ongoing research is needed to unravel the aetiology of dyspepsia on a molecular basis. Although this has not been matter of study in this thesis, we believe that a successful treatment can only be found after elucidation of its aetiology.

If we would have the possibility to repeat our large population survey, we would use a validated questionnaire and we would also perform non-responder research. In the ideal study, we would perform upper endoscopy and determination of Helicobacter pylori presence in every participant. To assess the association between medication use and gastrointestinal symptoms into more detail, we would question medication use into more detail; what drugs; what dose; how was the compliance, when was the drug started etc. To assess symptoms over time, we would send a second questionnaire 1 year after the first questionnaire.

Future studies on NSAID use and gastrointestinal complications should also focus on lesions in the lower gastrointestinal tract, as there is experimental evidence that suggests an increased proportion of lower gastrointestinal tract lesions in users of concomitant PPIs and NSAIDs.43 Ideally, an individual risk profile in NSAID users should be constructed based on gastrointestinal risk and cardiovascular risk scores. This is in line with the strategy of risk assessment in cardiovascular disease.

We expect that the role of Internet in our healthcare system will grow further in the future, which creates many new opportunities. We have shown a proof of principle, by studying feasibility to capture individuals with GERD symptoms through a dedicated website. We assume that this concept can be used for many other diseases. Another promising option, associated with our follow-up via the Internet, is monitoring of outpatients. This concept of telemonitoring has been most extensively studied in patients with heart failure.44-47 Results regarding improvement of hospital admission rates and overall
mortality are currently still ambiguous, but we believe that this method of follow-up will be optimized the next years and will be added to the arsenal of methods for patient-doctor communication.

REFLECTION

We believe a Discussion section of a thesis can also be used to reflect on the work we have done over the past few years. Although large questionnaire-based studies have been performed multiple times in the past and were widely accepted, we faced several struggles. As discussed in the section above, we would certainly change the study design if we would be able to perform this study again.

Due to a changed research environment in gastroenterology with advent of novel technologies, gene studies and new drugs, we experienced that epidemiological studies on gastrointestinal symptoms have low priority for Journal editors. We also experienced that the willingness of randomly selected Dutch inhabitants to complete and return the questionnaire was limited, which resulted in a response rate of 35%. This percentage consistently raised questions about selection bias by reviewers, which we were not able to refute due to our study design. The design did not allow us to perform non-responder research. Therefore, we will be reluctant to use this study model again in future epidemiological studies.

We used a non-validated questionnaire, which was used in several studies in the past and was improved step-by-step. However, use of a validated questionnaire to assess gastrointestinal symptoms would have improved the use and incorporation of widely accepted diagnostic criteria for functional gastrointestinal diseases, as the Rome III criteria. It would have facilitated the positioning of our results in respect to others.

As we focused on medication use as determinant of gastrointestinal symptoms, we could have further improved our data by asking respondents to report their current medication use. If we would be able to perform this study again, we would certainly change the study design.

Despite all these considerations, we feel that an update about the gastrointestinal symptom prevalence was warranted and this thesis adds valuable knowledge about this topic.

REFERENCES

Chapter 10


Chapter 11

English summary

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

Thesis series of the Institute for Genetic and Metabolic Disease
ENGLISH SUMMARY

We studied the current prevalence of gastrointestinal symptoms in the general population and the contribution of certain risk factors. In the past, similar studies have been performed, but factors associated with presence of gastrointestinal symptoms have changed over time, making these results outdated. Although gastrointestinal symptoms do not immediately lead to mortality, they are responsible for a decreased health-related quality of life. In addition, gastrointestinal symptoms significantly impact at a macro-economical level by healthcare visits, medication use, and additional investigations.

PART 1 PREVALENCE AND IMPACT OF GASTROINTESTINAL SYMPTOMS

Chapter 1 (General Introduction) describes background information regarding gastrointestinal symptoms, including pathogenesis, clinical evaluation and therapeutic options. We also describe the three models that we have employed to answer our research questions: a questionnaire-based model, a systematic review, and a prospective intervention study. In Chapter 2 we describe the results of 51,869 questionnaires, which we sent to randomly selected Dutch inhabitants of five municipalities: Nijmegen, Wičhen, Malden, Den Haag and Almere. We chose these communities to obtain a representative geographical distribution; east versus west, village versus city. In total, 18,317 questionnaire respondents were returned (response rate 35%) of which 16,758 were eligible for analysis. A total of 26% reported presence of gastrointestinal symptoms. Individuals with these symptoms reported a decreased health-related quality of life compared to individuals without gastrointestinal symptoms (EQ 5D score 0.81 (SD 0.21), vs 0.91 (SD 0.14), p < 0.01). After correction by multivariable analysis, female gender and asthma/COPD were independently associated with gastrointestinal symptoms. Also, use of paracetamol, antidepressants and acid-suppressive medication was associated with these symptoms. Advanced age and use of statins were associated with a decreased risk for gastrointestinal symptoms.

In Chapter 3 we describe the results about presence of gastroesophageal reflux disease (GERD) in website visitors of a dedicated GERD website (www.maagzuur.nl, “maagzuur” is “gastric acid”) who completed the GerdQ self-assessment questionnaire. A GerdQ score of ≥ 8 is suggestive for GERD. In 2.5 years, more than 150,000 individuals completed this questionnaire, and 80% did not report proton pump inhibitor (PPI) use. In this group of non-PPI users, 64% had a GerdQ score ≥ 8, of which almost half (48%) reported high impact of GERD symptoms on daily life by use of over-the-counter (OTC) acid-suppressive medications and sleep problems do to heartburn and/or regurgitation. In the group of PPI users, 88% reported GERD symptoms more than one day per week. Respondents with GERD symptoms reported a decreased health-related quality of life compared to individuals without symptoms.

In Chapter 4 we describe the results of a prospective observational study among respondents who completed the GerdQ self-assessment questionnaire at baseline, and after 4, 12 and 24 weeks. Our main finding is that 66% of respondents who did not use PPIs at baseline reported symptom improvement after 24 weeks. Based on these findings, we recommend adherence to the Dutch guideline ‘GERD’, which advises lifestyle changes as first step in patients who present with symptoms suggestive for GERD, instead of prescription of acid-suppressive medication. We also followed PPI users and found that over 90% reported persistence of symptoms for more than one day per week after 24 weeks. A drawback of online research, we experienced, is a high dropout of respondents during follow-up.

PART 2 DETERMINANTS OF GASTROINTESTINAL SYMPTOMS

Chapter 5 describes the results of a systematic review of current guidelines and consensus agreements regarding risk factors for gastrointestinal complications in nonsteroidal anti-inflammatory drug (NSAID) users. Nine guidelines were eligible for inclusion. We found that a history of (complicated) peptic ulcer disease, older age, concomitant anticoagulant, low-dose aspirin and systemic corticosteroid use and use of multiple NSAIDs were clearly defined as a risk factor in all guidelines. A history of gastrointestinal symptoms, use of high dose NSAIDs, concomitant use of clopidogrel or selective serotonin reuptake inhibitors (SSRIs), presence of severe rheumatoid arthritis disability, and cardiovascular disease were seen as risk factor for gastrointestinal complications in one or more guidelines. Presence of Helicobacter pylori is regarded an additive risk factor, as the exact role of this factor in the aetiology of NSAID-associated gastrointestinal ulceration is still under debate. We also assessed statements regarding OTC NSAID use in the studied guidelines and concluded that the information regarding OTC NSAID use was limited.

We assessed gastrointestinal symptoms in prescribed and OTC NSAID users in Chapter 6. NSAID users more frequently reported gastrointestinal symptoms compared with respondents that did not use NSAIDs (33% vs 24%, p < 0.01). We did not find a difference in gastrointestinal symptom presence between users of prescribed and OTC NSAIDs after adjustment for confounders. In users of prescribed NSAIDs at risk for gastrointestinal complications, only 51% concomitantly used a PPI. In Chapter 7 we report on the effectiveness of PPIs to reduce NSAID-associated upper gastrointestinal symptoms in a prospective, open-label study in primary care. Eighty-one percent of participants reported complete or partial response with PPI therapy. This study demonstrates that PPIs can be used to reduce NSAID-associated upper gastrointestinal symptoms in daily clinical practice.
In Chapter 8 we studied gastrointestinal symptoms in users of plain aspirin and carbasalate calcium through a large questionnaire-based study in the general population. We could not confirm the hypothesis that use of carbasalate calcium is associated with less gastrointestinal symptoms. Based on our results, plain aspirin remains the drugs of first choice for secondary prevention in cardiovascular disease.

Antidepressants are frequently used medications and gastrointestinal symptoms are frequently reported side effects. Simultaneously, antidepressants are also a treatment modality in functional gastrointestinal disorders. In Chapter 9 we assessed the association between antidepressant use and gastrointestinal symptoms in the general population. Gastrointestinal symptoms were more frequently reported by antidepressant users compared to non-users (40% vs. 25%, p < 0.01). However, after correction for confounding by multivariable analysis, no association between antidepressant use and gastrointestinal symptoms was found. We assume that the univariable association may be attributable to bias, for example by the presence of depressive symptoms.

In conclusion, the current population prevalence of gastrointestinal symptoms is still high and is associated with a decreased health-related quality of life. Given the large individual and societal impact, improvement of treatment options of these symptoms would be worth pursuing. Gastrotoxic drugs, as NSAIDs, are associated with presence of gastrointestinal symptoms. When patients present with these symptoms, we suggest that medication use deserves careful evaluation. If possible, gastrotoxic drugs should be stopped or the dose of these agents should be lowered.

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DEEL 1 PREVALENTEE EN GEVOLGEN VAN GASTRO-INTESTINALE KLACHTEN

Hoofdstuk 1 (Introductie) geeft een overzicht van de achtergronden van gastro-institinale klachten, de theorieën over de etiologie van deze klachten en de behandelmogelijkheden. Tevens worden in dit hoofdstuk de drie modellen beschreven die in dit proefschrift gebruikt zijn om de onderzoeksvragen te beantwoorden: vragenlijstonderzoek, een systematische review, en een prospectieve interventiestudie. In Hoofdstuk 2 beschrijven we de uitkomsten van de 51.869 vragenlijsten die gestuurd zijn naar willekeurig selecteerde inwoners van Nijmegen, Wijchen, Malden, Den Haag en Almere om een goed beeld te krijgen van de huidige prevalentie van gastro-intestinale klachten in Nederland. Een totaal van 18.317 vragenlijsten is teruggestuurd (respons van 35%), waarvan er 16.758 geschikt waren voor analyse. Zesentwintig procent van deze respondenten meldde gastro-intestinale klachten. Individueel aanpassing voor verstorende factoren (confounding) via multivariaat analyse, vonden we dat vrouwen en rokers een hogere prevalentie hadden van de drie huidige prevalenties die het voorkomen van deze klachten in de populatie onderzocht hebben. Echter, veel factoren die van invloed zijn op deze klachten, zijn in de loop van de tijd veranderd, zoals de prevalentie van Helicobacter pylori en het gebruik van gastrotoxische medicatie. Hierdoor zijn de oude cijfers wellicht niet meer toepasbaar. Gastro-intestinale klachten zijn gelukkig niet geassocieerd met een verhoogde mortaliteit, maar ze gaan wel gepaard met een verklaard kwaliteit van leven. Tevens zijn ze verantwoordelijk voor substantiële gezondheidszorgkosten, onder andere door artsbezoek, medicijengebruik, en aanvullend endoscopisch onderzoek.
individen deze vragenlijst ingevuld, waarvan 80% geen maagzuurremmers (PPRs) gebruikte. Van deze groep zonder PPI gebruik voldeed 64% aan de criteria voor refluxziekte (gedefinieerd als GerDQ score ≥ 8). Bijna de helft van niet-PPI gebruikers met refluxklachten (48%) gaf aan dat de klachten veel invloed hadden op het dagelijks leven. Van de respondenten die wel een PPI gebruikten, rapporteerde 88% minimaal 2 dagen per week klachten. We vonden in deze studie dat refluxklachten geassocieerd zijn met een verminderde kwaliteit van leven in vergelijking met respondenten zonder klachten. In Hoofdstuk 4 beschrijven we de resultaten van de studie waarbij we respondenten die de GerDQ vragenlijst invulden, gedurende 24 weken hebben gevolgd. Onze belangrijkste bevindingen zijn dat 66% van de respondenten die geen PPI gebruikten, een vermindering van klachten rapporteerden aan het einde van de follow-up. De overgrote meerderheid van de PPI gebruikers daarentegen had na 24 weken nog steeds klachten. Op basis van deze getallen, raden wij aan de Nederlandse richtlijn te volgen, zodat patiënten die voor de eerste maal met refluxklachten bij de huisarts komen, niet direct maagzuurremmen voorgeschreven krijgen. Tijdens deze studie ondervonden we dat bij online onderzoek een groot deel van de respondenten de vervolgvragenlijsten niet invult. Hierdoor voldeden helaas veel respondenten niet aan de inclusie criteria voor deze follow-up studie.

DEEL 2 DETERMINANTEN VAN GASTRO-INTESTINALE KLACHTEN

In Hoofdstuk 5 beschrijven we de resultaten van een systematische review naar Engels-talige richtlijnen en consensusdocumenten over risicofactoren bij NSAID gebruik (NSAID staat voor “nonsteroidal anti-inflammatory drug”). Negen richtlijnen voldeden aan onze selectiecriteria en werden geïncludeerd. Op basis van deze richtlijnen, concluderen we dat bij een voorgeschiedenis met ulcuslijden, een hogere leeftijd, het gelijktijdig gebruik van anticoagulantia, systemische corticosteroiden, lage dosis aspirine en het gebruik van meerdere soorten NSAIDs uniform geadviseerd wordt om een maagbeschermende (gastroprotectieve) strategie toe te passen. Een voorgeschiedenis van gastro-intestinale klachten, een hoge dosis NSAIDs, gelijktijdig gebruik van clopidogrel of een selectieve serotonine-heropnameremmer (SSRI), ernstige reumatoïde artritis en hart- en vaatziekten waren risicofactoren voor gastro-intestinale complicaties die in een of meerdere richtlijnen genoemd werden. Een infecctie met Helicobacter pylori beschouwen we als een bijkomende risicofactor. De specifieke bijdrage van deze bacterie in het ontstaan van NSAID-geassocieerde gastroduodenale ulceraties en bloedingen is nog niet geheel uitgekristalliseerd. We onderzochten tevens in hoeverre het gebruik van vrij verkrijgbare (over-the-counter; OTC) NSAIDs in deze richtlijnen geïntegreerd is. In de bestudeerde richtlijnen was hierover echter weinig informatie te vinden. In Hoofdstuk 6 hebben we gastro-intestinale klachten bij NSAID gebruikers onderzocht, waarbij we gebruikers van deze medicatie op recept hebben geilekeken met respondenten die OTC NSAIDs gebruikten. NSAID gebruikers hebben vaker gastro-intestinale klachten dan mensen die geen NSAID gebruiken (33% vs 24%, p < 0,01). We vinden echter geen verschil tussen beide soorten NSAID gebruikers (voorgeschreven vs. OTC) na correctie voor confounders. Slechts 50% van de gebruikers van voorgeschreven NSAIDs met een verhoogd risico op gastro-intestinale complicaties gebruikte gelijktijdig een PPI. We hebben in Hoofdstuk 7 via een prospectieve open-label studie in de huisartsenpraktijk onderzocht of PPIs effectief zijn in de behandeling van NSAID-geassocieerde gastro-intestinale klachten. We vonden dat bij 81% van de patiënten sprake was van verbetering of zelfs volledig verdwijnen van de klachten. PPIs kunnen dus in de dagelijkse praktijk gebruikt worden voor reductie van gastro-intestinale klachten bij NSAID gebruikers.

In Hoofdstuk 8 hebben we onderzocht of er verschil is in gastro-intestinale klachten tussen gebruikers van lage dosis aspirine en ascal via de vragenlijststudie in de algemene bevolking. We vonden dat 81% van de patiënten met een verlangd risico op gastro-intestinale complicaties NSAID gebruiken en voorgeschiedenis van gastro-intestinale klachten en infectie met Helicobacter pylori en infectie met NSAID in deze richtlijnen geïntegreerd is. De hypothese dat ascal minder gastro-intestinale klachten veroorzaakt dan aspirine, omdat dit geneesmiddel minder lokale maagschade zou geven, kon niet worden bevestigd. Wij zijn dan ook van mening dat ascal niet het middel van eerste keuze dient te zijn bij secundaire preventie voor hart- en vaatziekten.

Antidepressiva zijn veelgebruikte geneesmiddelen, die enerzijds gastro-intestinale klachten kunnen induceren, aangezien dit vaak gerapporteerde bijwerkingen zijn. Anderzijds worden antidepressiva tegenwoordig ingezet als tweedelijns behandeling bij functionele klachten van het maagdarmstelsel. In Hoofdstuk 9 hebben we onderzocht of antidepressivagebruik in de algemene bevolking geassocieerd is met gastro-intestinale klachten. Bij univariate analyse vinden we dat antidepressivagebruikers significant vaker klachten rapporterden dan niet gebruikers (40% vs. 25%, p < 0,01). Echter, na multivariaat analyse verwijdt de associatie tussen antidepressiva gebruik en gastro-intestinale klachten. We denken dan ook dat de univariate associatie veroorzaakt wordt door bias, zoals de aanwezigheid van depressieve klachten.

Samenvattend concluderen we dat de populatieprevalentie van gastro-intestinale klachten nog steeds hoog is en geassocieerd is met een verminderde kwaliteit van leven. Gezien de grote individuele en maatschappelijke impact, is winst te behalen door een verbeterde behandeling van deze klachten. Aangezien gastrotoxische medicijnen, zoals NSAIDs, een rol kunnen spelen bij de etiologie van deze klachten, dient geïnformeerd te worden, of deze medicatie gestaakt of verminderd kan worden in het geval dat een patiënt zich met deze klachten prenteert.
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Merel Tielemans (28 november 1983) groeide op in Helvoirt (Noord-Brabant). Na het behalen van het Gymnasium diploma op Gymnasium Beekvliet te Sint-Michielsgestel, startte zij in 2002 met de studie Geneeskunde aan de Radboud Universiteit te Nijmegen. Tijdens haar opleiding volgde zij een cursus Tropical Medicine in Caïro (Egypte) en was ze gedurende drie maanden werkzaam in Berekum (Ghana).


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