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Proton pump inhibitors: indications and acid rebound

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ABSTRACT

Proton pump inhibitors: indications and acid rebound

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Proton pump inhibitors (PPIs) are nowadays the therapy of choice in the management of a variety of upper gastrointestinal (GI) conditions particularly gastroesophageal reflux disease (GERD). Previous studies indicate that patients commonly receive PPIs without clear indications. The proportion of GERD patients refractory to PPI treatment is unclear. The clinical importance of acid rebound is controversial.

The aims of the present study were to evaluate the use and indications for PPIs in hospitalised patients and to assess the prevalence of GI symptoms in patients with chronic obstructive pulmonary disease (COPD). Furthermore, to assess the proportion of GERD patients with persistent symptoms despite high dose PPI therapy and to evaluate if cessation of PPI therapy in healthy subjects is associated with the development of GI symptoms.

The use of PPIs was evaluated by reviewing medical records, and by interviewing patients. Gastrointestinal symptoms and psychological well-being in COPD patients were assessed by using three questionnaires: the Gastrointestinal Rating Scale, the Psychological General Well-Being and the Hospital Anxiety and Depression scale. GI symptoms and quality of life in GERD patients were measured using four questionnaires: the Reflux Disease Questionnaire, the GERD Impact Scale and the SF-36. To assess upper GI symptoms in healthy volunteers after cessation of therapy the Glasgow Dyspepsia Questionnaire was used. Gastrin and chromogranin-A (CgA) were used as indirect measures of gastric acid inhibition.

A large proportion of hospitalised patients used PPIs. Among hospitalised pulmonary patients 49% used PPIs and the majority of the indications for the use were inappropriate, with peptic ulcer prophylaxis during corticosteroid therapy being the dominating inappropriate indication. The dominating appropriate indication was treatment for GERD. Gastroscopy had only been performed in 32% of patients.

Gastrointestinal symptoms were common in patients with COPD but similar to another chronic patient group (chronic renal failure). The GI symptoms were associated with impaired psychological general well-being. COPD patients treated with PPIs had higher GI symptom severity and lower general well-being than patients not using PPIs.

GERD patients with at least moderate reflux symptoms despite PPI treatment were common. However, persistent symptoms are rare after increased dosage of PPI therapy.

Discontinuation of a four week course of PPIs in previously healthy subjects was associated with significantly higher frequencies of upper GI symptoms during the first and second week after cessation of therapy compared with subjects receiving placebo, 44% vs 9% respectively ($p<0.001$). Significant higher levels of fasting as well as meal stimulated gastrin and CgA levels were found on the last day of treatment compared with levels prior to treatment. The GI symptoms during the first week after treatment correlated with basal and stimulated gastrin levels at the end of treatment.

Conclusion: PPIs were commonly used by hospitalised patients, and were especially common among pulmonary patients. A high proportion of patients lacked an adequate indication for PPI use. Few patients with GERD are refractory to treatment with PPI after increased PPI dosage. Cessation of PPI therapy in healthy asymptomatic subjects seems to induce GI symptoms. These symptoms are related to the degree of acid inhibition and are probably due to acid rebound hypersecretion.

Key words: Proton pump inhibitors; indications; gastrointestinal symptoms; overuse; chronic obstructive pulmonary disease; acid rebound hypersecretion; gastroesophageal reflux disease.

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Till *Familjen*

Nog finns det mål och mening i vår färd -
men det är vägen, som är mödan värd.

Karin Boye *"I rörelse"*

Proton pump inhibitors: indications and acid rebound

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LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals.

I. **Overuse of acid suppressive therapy in hospitalised patients with pulmonary diseases.**
Niklasson A, Bajor A, Bergendal L, Simrén M, Strid H, Björnsson E.
Respiratory Medicine 2003; 97: 1143-50.

II. **Prevalence of gastrointestinal symptoms in patients with chronic obstructive pulmonary disease.**
Niklasson A, Strid H, Simrén M, Engström CP, Björnsson E.
European Journal of Gastroenterology 2008; 20: 335-41.

III. **Quality assessment of patients with Gastroesophageal reflux disease treated with proton pump inhibitors: impact of high dose therapy.**
Niklasson A, Sager-Lund C, Tillander L, Kilander A, Björnsson E.
In manuscipt

IV. **Dyspeptic symptom development after discontinuation of a proton pump inhibitor: A double-blind placebo-controlled trial.**
Niklasson A, Lindström L, Simrén M, Lindberg G, Björnsson E.
Submitted for publication

CONTENTS

ABBREVIATIONS

AST	Acid-suppressive therapy
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CgA	Chromogranin-A
ECL	Enterochromaffin-like cell
FEV1	Forced Expiratory Volume in one second
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
GIS	GERD Impact Scale
GSRS	Gastrointestinal Symptom Rating scale
H.*pylori*	Helicobacter pylori
HAD	Hospital Anxiety and Depression Scale
IBS	Irritable Bowel Syndrome
IQR	Interquartile range
NSAID	Non-Steroidal Anti-Inflammatory Drug
NERD	Non erosive reflux disease
NS	Non-significant
PPIs	Proton Pump Inhibitors
PGWB	Psychological General Well-Being
RDQ	Reflux Disease Questionnaire
SD	Standard Deviation
vs.	Versus

INTRODUCTION

Acid related complaints are frequent and 10 to 20 % of the general population experience heartburn and/or regurgitation at least once a week (1-7). Within a year 25-54 % of all adults in the general population will have experienced dyspeptic symptoms, but only a few of these will seek medical care (8-11). Among those dyspeptic patients who seek medical care the main findings are functional dyspepsia (>50%), peptic ulcer disease (20%), gastroesophageal reflux (20-30 %) or gastric carcinoma (<2%) (12). Proton pump inhibitors (PPIs) have become the choice of therapy in the management of acid related complaints, including gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) as well as duodenal and gastric ulcers (13). Proton pump inhibitors represent one of the most commonly prescribed classes of drugs both in hospital and primary care settings (14-16). The usage of these drugs are increasing and constitute approximately 5-11 % of the total medical budget in Western countries such as UK, Denmark and Sweden (17). Although dyspeptic and reflux symptoms are highly prevalent according to epidemiological surveys (18, 19), it is unknown if the increasing use of antisecretory medication is related to a change in occurrence of these acid-related conditions, or a change in prescribing patterns. It has been proposed that PPIs are more often nowadays prescribed for minor symptoms without a clear indication (15, 20). Knowledge regarding the type of patients who use acid secretory medication, why they use it, and the consequences of this usage is limited. Although PPIs are effective and safe medications, concerns have been raised about the rebound acid hypersecretion phenomenon which has been proposed to occur after cessation of treatment with PPIs (21-24). Rebound acid hypersecretion is defined as an increase in gastric acid secretion after cessation of therapy compared to the acid secretion before treatment (25). The clinical significance of this proposed acid rebound phenomena remains unknown. Another challenge in the management of acid suppressive disorders is how to treat patients that do not respond adequately to PPI treatment. It has been reported that the number of GERD patients not responding to treatment with PPIs (refractory) (26, 27).

1. GASTRIC ACID

The role of gastric acid in the stomach is to kill micro-organisms, including viruses (28). Gastric acid also plays an important role in the digestion of proteins. However, gastric acid can also cause problems and plays a major pathogenic role in upper gastrointestinal diseases such as reflux esophagitis.

1.1 The parietal cell and the acid secretory process

Gastric acid is produced in the stomach by the parietal cells. The normal human stomach contains approximately 1 billion parietal cells, with the number of parietal cells determining the maximal secretory rate and accounting for the variability among individuals (29). The parietal cells are located in the middle and lower parts of the gastric glands in the oxyntic part of the stomach. Secretion of acid from the parietal cell into the lumen is an energy demanding process where the parietal cell must expend a large amount of energy to concentrate hydrogen ions. This energy comes from adenosine triphosphate (ATP) which is produced by the numerous mitochondria located within the cell. When the parietal cell pumps H^+ into the lumen it is exchanged for K^+ across the mucosal membrane (30). This active transport is catalysed by the H+, K+-ATPase, and is called the gastric proton pump, and the proton pump is the final step of acid secretion (Figure 1).

1. 2 Stimulants of acid secretion

Acid secretion by the parietal cell is a complex process regulated by paracrine, endocrine and neural pathways. The physiological stimuli include acetylcholine, gastrin and histamine. Acetylcholine stimulates gastrin release in addition to stimulate the parietal cell directly (29, 31, 32). Histamine occurring in many tissues including the entire GI tract is a potent stimulator of acid secretion. Histamine is found in the enterochromaffine-like (ECL) cell which is located close to the parietal cell. The mechanisms behind acid secretion are shown in Figure 1. Gastrin stimulates acid secretion by directly stimulating the parietal cell as well as stimulating the release of histamine from the ECL cell. Gastrin has a trophic effect on the ECL cell and regulates the ECL cells proliferation. Increased gastrin levels (hypergastrinemia) results in an increase in the number of ECL cells (hyperplasia) which in turn leads to an increase of chromogranin- A (CgA) in the blood (29, 31, 32).

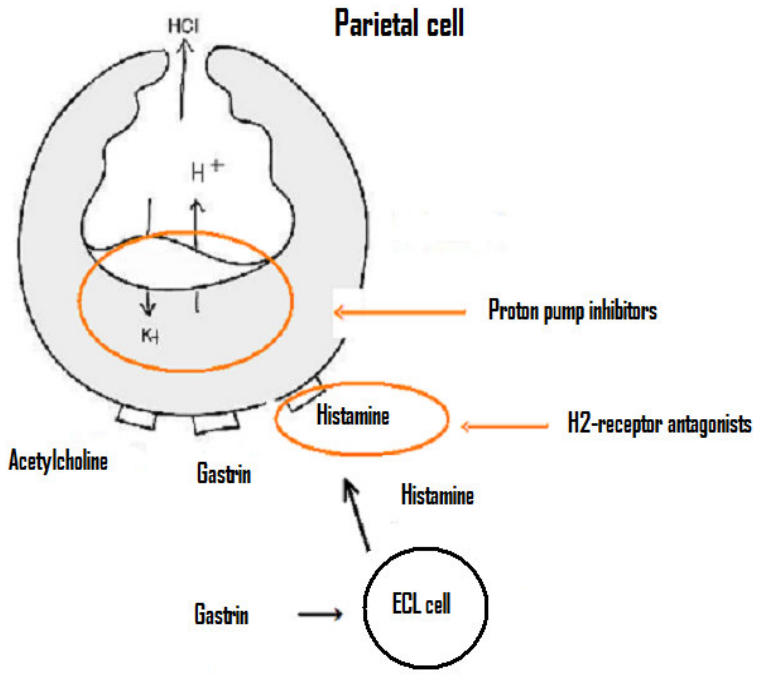

Figure 1. The parietal cell and the mechanisms of acid secretion.

2. GASTRIC ACID-SUPPRESSIVE THERAPY

2.1 Overview

More than a century ago the initial discovery of gastrin followed by that of histamine, lead to progress over the following century in unrevealing the acid peptic disorders, highlighted by an increasingly sophisticated understanding of their role in the regulation of acid secretion (33). During the past four decades a dramatic improvement in the management of acid related disorders has been accomplished. Firstly, the discovery of the histamine$_2$ receptor on the parietal cell (34) lead to the development of the histamine$_2$ receptor antagonists (H_2-receptor antagonists). Both of which were major landmarks in the treatment of acid related disorders (35). This was followed by the discovery of a proton pump inhibitor in the early eighties, which was another great step in the management of acid related disorders (36). Both H_2-receptor antagonists and PPIs are agents which inhibit acid secretion and the introduction of these agents was revolutionary in the treatment of acid disorder leading to a substantial improvement in quality of life for a large number of patients (13). These agents could heal peptic ulcer and surgery as a treatment for peptic ulcer disease has today mostly disappeared

(37). Proton pump inhibitors soon after marketing revealed a great efficiency in the treatment of GERD and are nowadays the drug of choice for most if not all acid related disorders.

2.2. H_2-receptor antagonists

The first H_2-receptor antagonist introduced on the market was cimetidine, followed by ranitidine, famotidine and nitrazidine. These agents are specific antagonists that inhibit gastric acid secretion by blocking the H2-receptor on the basolateral membrane of the parietal cell (Figure 1) (35). The H_2-receptor antagonists are not able to inhibit meal-induced acid secretion and are only suitable for acid suppression during periods of basal acid secretion (34) and dosage at bedtime is therefore recommended (38). Adverse reactions are relatively rare among H_2-receptor antagonists users, however there are some clinically important interactions between H2-antagonists and other drugs such as ketoconazole, metoprolol and theophylline. Another negative and restrictive factor in the use of H2-antagonists is the development of tachyphylaxis (tolerance) (39).

2.3 Proton pump inhibitors

The PPI group includes omeprazole, esomeprazole, lanzoprazole, pantoprazole and rabeprazole. These are effective acid-suppressive drugs that inhibit the final pathway for acid secretion in the parietal cell (Figure 1). All PPIs are substituted benzomidazole derivates and they function as pro-drugs and accumulate in the acid space of the parietal cell where they are converted to active sulphenamides by an acid catalysed reaction. By covalent binding, the sulphenamides inhibit the proton pump (H+/K+ATPase) irreversibly, resulting in a marked inhibition of both basal and stimulated gastric acid secretion (36). Proton pump inhibitors only bind to active proton pumps. Therefore only activated parietal cells will be inhibited, and resting parietal cell will escape inhibition (31). The ability of the parietal cell to secrete acid is restored when a new proton pump is converted from its inactive status in the tubulovesicle to the active form resulting in its location on the canalicular surface. As PPIs are most effective when the parietal cell is stimulated to secrete acid postprandially the timing of the dose is important. These drugs should be taken prior to a meal for optimal control of the acid secretion and to avoid therapeutic failure (40, 41). In most individuals, once-daily dosing is sufficient to produce the desired level of acid inhibition, however occasionally a second dose is necessary and should preferably be administered prior to evening meal.

Proton pump inhibitors are rapidly absorbed in the duodenum after oral administration with peak concentrations occurring two to four hours after administration (42). Since these drugs are acid-labile, they must be formulated in an enteric coating to avoid rapid degradation in the stomach (42). As PPIs bind irreversibly to the proton pump their duration of action is more affected by regeneration of new pumps than by the pharmacokinetic properties of the PPIs themselves. Proton pump inhibitors are metabolised by the polymorphic cytocrome P450 (CYP) system (43-45). Most PPIs are predominantly metabolised by the S-mephenytoin hydroxylase (CYP2C19) and to varying degrees by nifedipine hydroxylase (CYP3A4) (44, 46). However in contrast to the other PPIs, pantoprazole has a lower affinity to the CYP system (47-49). In addition to metabolism by the CYP system, pantoprazole is also metabolised by a cytosolic sulphotransferase with is neither non-saturable nor apart of the CYP system (44 141, 48 139, 49 140). The generic polymorphism of CYP2C19 is well studied, and three genotypes exist. They are heterozygous extensive (fast) metabolisers (EM), homozygous EM and metabolisers and poor (slow) metabolisers. About 3% of Caucasians are poor metabolisers, and approximately 47 % are heterozygous EM (50). Intragastric pH and gastrin levels during treatment with PPIs are influenced by the gene variations in CYP2C19. Intragastric pH and gastrin are shown to be higher in poor metabolisers and heterozygous EM than in homozygous EM (51). Although PPIs are often well tolerated in humans, the most common adverse effects reported for all PPIs include headache, diarrhoea, rash and nausea with an incidence of 1-3% (52).

As healing and symptom control in acid related disorders correlate well to the degree of acid suppression (53), the therapy of choice in the current management of acid related gastrointestinal disorders is PPIs. Proton pump inhibitors are first line therapy as they produce more complete and longer lasting acid suppression than H_2-receptor antagonists (31). Proton pump inhibitors also have a slightly more preferable safety profile with fewer interactions with other drugs when compared with H_2-receptor antagonists (13).

2.4 Indications for PPI use

Increased acid secretion is often found in patients with duodenal ulcer (54). Inhibiting the acid secretion heals the ulcer, and the more the secretion is inhibited, the quicker the healing process will be (55). In the case of peptic ulcer in the stomach, acid secretion is either normal or reduced (28). Nonetheless, inhibition of acid secretion heals the ulcer and reduction

relapses (55). Reduced acid secretion in peptic ulcer is caused by the accompanying gastritis (56). Peptic ulcers generally need a longer period of treatment before healing, compared with duodenal ulcers (55). It is today well accepted that *Helicobacter pylori (*H. *Pylori)* infection is an important factor in the development of peptic ulcer disease, particularly duodenal ulcer (57). Not all patients with peptic ulcer disease are H. *pylori* positive, but those who are benefit from an eradication regimen consisting of a PPI plus antimicrobial agents. A seven-day regimen is recommended by consensus guidelines (58).

There are a number of gastroduodenal mucosal defensive mechanisms, with non-steroidal anti-inflammatory drugs (NSAID) having deleterious effects on most of them. This results in a mucosa less able to cope with even a reduced acid load, such as during treatment with NSAIDs (59). Therefore adverse events that influence the GI tract are common among NSAID users, where the predominant GI side effects are gastroduodenal ulcers, erosions and dyspeptic symptoms (60). Proton pump inhibitors have shown to have a prophylactic effect against ulcers and dyspeptic symptoms in patients on long term treatment with NSAIDs (61, 62). Proton pump inhibitors are also used as NSAID prophylaxis in patients with certain risk factors (63).

Gastroesophageal reflux disease is among the most common gastrointestinal disorders in people in the Western world (1). The prevalence of GERD shows a range from 10% to 20 % in the general population depending on the definition and methodology used, although only a minority of these seeks health care (5, 64, 65). The diagnosis of GERD is usually based on a history of "typical" symptoms such as heartburn and acid regurgitation, with the symptoms ranging from mild to atypical, making diagnosis of this condition at time difficult. According to the Montreal definition GERD symptoms have to be troublesome or severe enough to cause a clinically significant impairment of the patient's health-related quality of life (66).
Maintaining an intragastric pH above 4 has been widely accepted as the benchmark for the efficiency of anti-secretory agents which are used in the treatment of pathological reflux (67). The degree of mucosal healing is directly related to the proportion of time during the 24-hour period for which the intragastric pH is maintained above 4. Distinct advantages in terms of healing and symptom relief have been shown for PPIs over H_2-receptor antagonists in the control of GERD symptoms as well as healing of esophagitis (68). Proton pump inhibitors offers, according to 33 randomised controlled trials, a healing rate of approximately 78% in patients with esophagitis (69).

Proton pump inhibitors are also used in the treatment of patients with Zollinger-Ellison syndrome. These drugs are also in some countries approved for treatment of ulcer-like symptoms. This indication is probably based on the results from the Bond and Opera studies, showing the benefit of PPI compared with placebo in patients with ulcer-like dyspepsia (70).

2.5 Non approved indications

The use of PPI for functional dyspepsia is common although the usage to manage dyspepsia is controversial. There is little evidence that excess acid secretion is involved in the aetiology of this condition (71), and the natural history of functional dyspepsia remains poorly defined (72, 73). It has been shown that the placebo response in functional dyspepsia is high and is at least 30 to 40 % (74). It has also been demonstrated that treatment with PPI has a limited therapeutic effect over placebo (70, 75). Patients with uninvestigated dyspepsia may according to some guidelines, be recommended a single dose therapy of H_2-receptor antagonists for 2-4 weeks to assess response in patients without alarm symptoms, and endoscopy is recommended only for the elderly and patients with persistent or rapidly recurring symptoms (12).

Proton pump inhibitors are often prescribed as ulcer prophylaxis together with corticosteroids in a variety of conditions treated with corticosteroids. There has been some controversy as to whether or not the use of corticosteroids is associated with an increased risk for peptic ulcer. Earlier data indicated that the use of corticosteroids associated with the development of peptic ulcer, although only in a minority of patients (76). Studies have however since then found no association between corticosteroid use and the development of peptic ulcer (77, 78). It has been demonstrated that only patients on corticosteroids that are concomitantly treated with NSAID are at increased risk for development of peptic ulcer as compared with patients taking only corticosteroids (77, 78).

The use of PPIs for the prevention of stress ulcers has been well-defined in critical care patients (79). In recent years this practice has become increasingly common in general internal medicine patients (15). With little or no evidence to support the PPI use, this usage for prevention of stress ulcer in general medicine patients is currently not recommended nor is it supported in the clinical literature (80, 81).

2.6 The use of PPI

The use of PPIs has increased dramatically over the past decades. As the use of PPIs has increased so too have the cost for these drugs, with today's cost for PPIs constituting a considerable part of the medical budget (82-86). In Sweden the conglomerate cost of PPIs has grown since these drugs were launched in 1988. During 2007 the total cost for PPIs was 0.8 billion SEK which constituted approximately 5 % of Sweden´s total medical budget. The expenditure on PPIs has recently decreased due to the reduction in the gross cost of PPIs. However the overall volume usage of these drugs is still increasing as measured by DDD (defined daily dosages) as shown in Figure 2. The DDD is a technical unit of measurement established by an expert panel and corresponds to the typical dose when the drug is used for its main indication by an adult. Today with the event of Helicobacter eradication therapy, the major part of PPI consumption can probably be attributed to reflux symptoms, although the proportion of patients using PPIs on the indication GERD vs other indications is unclear.

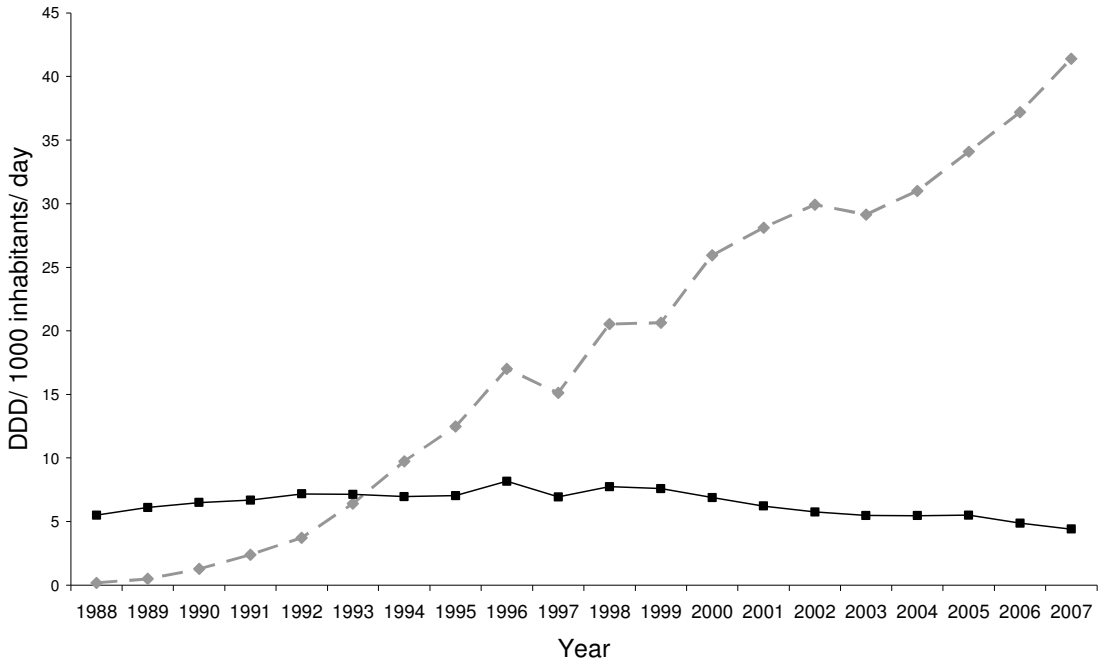

Figure 2. DDD /1000 habitants/day. Dotted lines represent the usage of PPIs, and the black lines represent the usage of H_2-receptor antagonists.

As for most drug classes, evolution in clinical practice with time has led to changes in the pattern of use. Firstly PPI became commonly used in the long-term maintenance of acid-related diseases particularly GERD (87, 88). Since then their use has extended into areas in which these drugs were not initially developed for. The alteration in this pattern of use may alter the balance between efficiency and those clinical problems related to their use i.e. the "risk/benefit ratio". There is today increasing evidence of both inappropriate prescribing and inappropriate use of these drugs, both in the hospital (14-16, 20, 89) settings and in general practice (90, 91). An expanding proportion of patients have indeed poor indications for the use of PPIs (82, 92). The use of acid suppressive therapy in specific patient groups has been largely unexplored.

2.7 Health related quality of life

Health related quality of life (HRQOL) measurements focus on the patient's subjective experience of the impact of the disease on their daily activities and well-being (93). Health related quality of life has become an important tool in assessing and explaining disease outcomes and has developed into an important outcome measure in treatment response of various diseases (94).

The health related quality of life in patients with GERD is significantly impaired compared with the general population (95, 96). Also the general population with upper GI symptoms has a worse HRQOL than those without symptoms (97-99). Symptoms of reflux disease negatively affect the HRQOL through their impact on physical, social and emotional aspects (95). Health related quality of life is associated with both symptom severity and changes in GERD related symptoms. Heartburn is the main symptom that influences HRQOL. It has been well documented that medical intervention in the treatment of GERD provides improvement in GERD-related symptoms as well as an improvement in well-being and HRQOL (100). A period as short as two weeks of treatment with PPI significantly improves the HRQOL in patients with GERD (96).

3. COPD AND GASTROINTESTINAL COMPLICATIONS

Chronic obstructive pulmonary disease (COPD) is a chronic, slowly progressive disease with airway obstruction (101). COPD is characterized by an accelerating decline in forced expiratory volume in one second (FEV1) and the relationship between COPD and smoking is very strong. Clinical relevant COPD within the Swedish adult population has been estimated to be from 4 to 6 % (102). However the prevalence is likely to be under-diagnosed (103). No major gender difference in prevalence has been found (102).

The anatomical and physiological relationship between the upper airway tract and the oesophagus consists of a complex interaction. In the settings of disease, pathophysiological alterations may reflect both the upper airway and/or the oesophagus (104). Patients with COPD may be more vulnerable to reflux due to exaggerated intrathoracic pressure shifts and increased frequency of cough diaphragmatic flattening, which are common features in patients with COPD (105).

Reflux-related symptoms are common in patients with asthma and several studies have estimated GERD symptoms in asthmatic patients to occur more often than in the general population (106-109). In contrast to asthma, limited data exists on the prevalence of GERD symptoms in patients with COPD (110-112). The prevalence of GERD in patients with COPD appears to be increased. It have been suggested that there is a trend towards a higher prevalence of GERD symptoms in patients with severe COPD (FEV_1 ≤50 %) compared to patients with milder COPD symptoms (FEV_1 >50%) (111, 112). However a recent study found no significant difference in the FEV_1 value between patients with GERD symptoms and those without GERD symptoms (113). Information regarding the occurrence and burden of other GI symptoms in COPD patients is incomplete. Previous studies have only compared COPD patients primarily with healthy subjects (110, 112), and not with patients with another chronic disease.

4. CHALLENGES ASSOCIATED WITH THE USE OF PPIs

As mentioned before PPI are an effective and safe treatment against acid related disorders, although a number of concerns have been raised regarding the usage of these drugs. Some studies have linked the use of PPI to an increased risk of community acquired pneumonia (114, 115), C difficile diarrhoea (116-118), campylobacter jejuni gastroenteritis (119) and hip fractures (120).

Other challenges in the use of PPIs include the management of patients with gastroesophageal symptoms who do not respond adequately to PPI therapy.

4.1 Patients refractory to PPI treatment

The vast majority of patients with erosive disease show complete healing of esophagitis (121) and improved quality of life when treated with PPIs (122). A significant proportion of GERD patients have however persistent symptoms despite therapy with PPIs. This is more commonly observed in patients with non-erosive reflux disease (NERD) (26, 123). In a survey of 11 000 patients with chronic heartburn only 58% reported being totally satisfied with their anti-reflux treatment (124). Approximately 30% (range 25-40%) of patients with GERD symptoms are either not completely satisfied with their therapy or their GERD symptoms persist in spite of PPI therapy (26). Inadequate response to PPI therapy among GERD patients has been reported to be increasingly encountered in both primary and secondary care (26, 27). Although patients with persistent problems despite acid suppressive therapy have been presented as a considerable problem, the PPI dose and duration of therapy is controversial before a patient is considered to be refractory to PPIs (125). The medical literature does not offer an accepted definition for PPI failure (126). The underlying mechanisms for PPI refractory reflux symptoms have not yet been fully identified. One important reason for treatment failure is lack of compliance, and in a study only 55 % of patients with GERD took their PPI once daily for 4 weeks as prescribed (127). A proposed mechanism is weakly acidity reflux. Weakly acid reflux is the reflux of gastric content into the oesophagus with a pH between 4 and 7. It has been suggested that weakly acid reflux is associated with classic GERD symptoms (128). Another possibly mechanism is visceral hypersensitivity (126).

In conclusion: little is known about the natural history of GERD patients that report symptoms despite receiving PPI therapy. Furthermore, limited data exist on the proportion of

symptomatic GERD patients that respond to the commonly used strategy in clinical practice of increasing the PPI dose in this scenario.

4.2 Rebound acid hypersecretion

It has been shown that discontinuation of acid suppressive therapy (AST) can lead to rebound acid hypersecretion. Rebound acid hypersecretion is defined as an increase in gastric acid secretion above pre-treatment levels following discontinuation of AST (25). Rebound acid hypersecretion after withdrawal of H_2-receptor antagonist treatment is today a well-established phenomenon (129-135). The rebound phenomenon after H_2-receptor antagonist withdrawal occurs during 2-10 days after withdrawal (129, 131-134).

The issue as to whether occurrence of rebound acid hypersecretion also applies after withdrawal of PPI therapy has been addressed in a number of studies (22-24, 135-139). However these studies present conflicting data some studies have found no evidence for rebound acid hypersecretion after discontinuation of PPI therapy (136-139). More recent studies suggest that there is an increase in acid secretory capacity after PPI therapy discontinuation in *H. pylori*-negative subjects (22-24).

H. pylori-positive subjects are less likely to experience rebound problems and this is probably due to the interaction between *H. pylori* colonization and acid production. *H. pylori* positive subjects have a mucosal inflammation which releases inflammatory mediators such as interleukin-1. Interleukin-1 is a potent suppressor of the production of gastric acid, and it is also suggested that the bacteria have a direct suppressive effect on the parietal cells (140, 141). Rebound phenomena in *H. pylori* positive patients may be masked at least two weeks after treatment by persisting oxyntic gastritis (142, 143).

The exact mechanism of the acid rebound phenomenon remains unknown, however there are four proposed mechanisms for the acid rebound hypersecretion. These are: upregulation of H_2 receptors, hypergastrinaemia-stimulating histamine release by ECL cells, increase of parietal cell mass, and upregulation of H+/K+-ATPase activity (39, 131, 132, 144-146). The development of ECL hypergastrinemia is probably associated with treatment duration since it takes some time to develop hyperplasia. Proton pump inhibitors block the proton pump irreversibly taking a number of days to generate fully. Therefore the rebound acid hypersecretion might be expected first after a number of days after cessation. The duration of rebound acid hypersecretion remains unknown, however it is suggested that after treatment

for 4-12 months the rebound hypersecretion measured with gastric acid output studies has lasted for at least 8 weeks but less than 26 weeks (21, 22, 137). Studies have suggested that CgA is useful in the evaluation of ECL-hyperplacia (24), as well as the possibility of gastrin being used to measure the rebound acid hypersecretion (25, 147).

The rebound acid hypersecretion after withdrawal of PPI therapy has been proposed to lead to difficulties for some patients in ceasing treatment with PPIs (148). This might be due to the resurgence of symptoms induced by acid rebound hypersecretion. The discontinuation of H_2-receptor antagonist is accompanied by the onset of dyspeptic symptoms in previously asymptomatic subjects (148). According to this hypothesis rebound acid hypersecretion may lead to a physical ”dependency” of acid suppressive therapy. Although many studies have been performed to evaluate the rebound of acid after withdrawal of PPIs, the clinical relevance of rebound hypersecretion after treatment with PPI remains unknown.

AIMS OF THE PRESENT STUDIES

The present thesis had the following aims:

1. To evaluate the use and indications for acid suppressive therapy in hospitalised patients and to investigate whether prescribing of acid suppressive medications follow the appropriate registered indications in three different wards at a large Swedish University hospital.

2. To assess the prevalence of gastrointestinal symptoms in patients with chronic obstructive pulmonary disease in comparison with patients with another chronic disease. Further to explore a relationship between gastrointestinal symptoms and psychological well-being among patients with chronic pulmonary disease.

3. To assess the proportion of GERD patients with persistent symptoms in spite of therapy with proton pump inhibitors and to assess the natural history of these complaints. To evaluate if a period of high dose therapy with PPI can resolve problems for patients refractory to PPI therapy.

4. To investigate whether healthy volunteers experience upper gastrointestinal symptoms after cessation of a short course of PPI treatment in comparison with placebo. To study a potential relationship between the possible symptoms and the gastrin and chromogranin-A levels.

SUBJECTS AND METHODS

The studies were all performed according to the Declaration of Helsinki and were approved by the ethics committee of the University of Göteborg. The study IV was also approved by the Medical Product Agency in Sweden. All participants in the studies gave their informed consent. This chapter presents and comments on the methods used for these studies. For further details see the separate papers (I-IV).

1. SUBJECTS AND INCLUSIONS CRITERIA

These studies were carried out between 2001 and 2007 at the Sahlgrenska University Hospital, with the exception of paper IV where the study occurred at both Sahlgrenska University Hospital and Karolinska University Hospital in Stockholm.

Paper I

A total of 301 hospitalised patients at the Sahlgrenska University hospital were included in the study. Out of the total 301 patients 162 patients were hospitalised on a pulmonary ward of which patients with pulmonary diseases were enrolled. A group of 139 patients served as controls. Of these 139 patients, 88 were hospitalised on a surgical ward, and 51 were hospitalised on the general medicine ward.

Paper II

A total of 234 outpatients with a diagnosis of COPD were consecutively recruited from the speciality pulmonary clinic at Sahlgrenska University Hospital, Gothenburg, Sweden. Of the 234 patients, 150 patients were eligible to participate. All patients had a diagnosis of COPD.
The inclusion criteria were diagnosis of COPD according to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) criteria (16), and age ≤80 years. Exclusion criteria were; patients with respiratory disorders other than COPD, significant co-morbidities such as malignancy, heart failure, rheumatoid arthritis, a poor command of the Swedish language, and any psychiatric disorder. A total of 113 patients completed the questionnaires, giving a response rate of 80%. Eighty-two patients with CRF served as a control group, and these patients were obtained from a group of 230 patients, who had previously been included in an

earlier study, conducted by our research group (149). The CRF control group was matched by age and gender to the patients with COPD. For comparison of GSRS and PGWB, we used values from a previous study on the general population which including 2.162 healthy subjects (150).

Paper III

A total of 123 patients were identified from two primary care centres in Gothenburg Sweden and from an endoscopy unit at the Sahlgrenska University Hospital in the same city with a diagnosis of GERD and on treatment with acid suppressive therapy. These subjects were asked to complete a questionnaire concerning the type, dose and duration of acid suppressive therapy, previous investigations and the pattern of drug use. A total of 88 of the 123 patients approached for the study (71.5%) completed the questionnaire.

Paper IV

Forty-eight, *H. Pylori*-negative healthy volunteers was included in the study. All included volunteers were non-smokers. None of the subjects had any previous history of gastrointestinal symptoms. Exclusion criteria were a positive *H. pylori* test, a history of dyspeptic symptoms, and the use of any agent that may induce dyspepsia such as i.e NSAIDs.

2. QUESTIONNAIRES (II, III, IV)

In the studies II, III and IV a range of self-administered questionnaires were used to assess GI symptoms, psychological state and quality of life.

Gastrointestinal Symptom Rating Scale (GSRS) (II) is a validated self-administered questionnaire (151), originally constructed as an interview-based rating scale (152). The GSRS measures the presence and severity of gastrointestinal symptoms. The GSRS uses a 7-graded Likert scale ranging from “no discomfort” to “very severe discomfort”. It includes 15 items which are grouped into five dimensions; reflux syndrome, abdominal pain syndrome, constipation syndrome, indigestion, and diarrhoea syndrome. The higher the scores, the more severe are the symptoms. The questions concern symptom severity relating to the last week previous to the questionnaire being filled out. The results from the GSRS were compared with normal values from the Swedish general population obtained in a previous study in which 2162 healthy subjects were enrolled (150). A second control group of 82 patients with chronic

renal failure previously recruited for a study by our research group were used as another control group. The data from this has been published earlier (149).

The Hospital Anxiety and Depression Scale (HAD) (II) was developed to detect depression and anxiety in patients with somatic disorders rather than in psychiatric patients (153). It is a reliable instrument with "cut-off" scores for screening of clinically significant anxiety and depression in outpatients attending a general medical clinic. This instrument has also been shown to be a valid measure in the severity of these disorders of mood. The self-assessment scale consists of 14 items, each using a four-grade Likert scale (0–3), with subscales for anxiety (seven items) and depression (seven items). A higher score represents a higher level of depression and anxiety. A score of eight or greater indicates possible distress and a score of ten or more indicates a clinical relevant depression and anxiety.

Rome II questionnaire (II). This questionnaire was designed in order to identify patients with functional GI disorders, such as irritable bowel syndrome (IBS) (154). These questions concern symptoms during the three month period prior to the study. The criteria are abdominal discomfort or pain with two of three of the following features; relieved with defecation and/or onset associated with a change in frequency of the stool, and/or onset associated with a change in the form (appearance) of the stool.

Comments: We used the Rome II, and the questions regarding IBS in order to identify patients who met the criteria for IBS.

Glasgow Dyspepsia Questionnaire (IV) was initially developed to provide a global measurement of the severity of dyspepsia in patients with a variety of upper GI disorders (155). A modified version of the Glasgow Dyspepsia Questionnaire was developed and used in an earlier study by Smith et al assessing symptom development in healthy volunteers after discontinuation of ranitidine (148). The modified Glasgow Dyspepsia Questionnaire was designed to reflect on a wide range of symptom severity and nocturnal disturbance as well as behavioural response to sustained symptoms (Table 1). A Swedish version of this questionnaire was used in study IV (Table 2).

Table 1. Modified version of the Glasgow Dyspepsia Questionnaire

Symptom Score		
Have you experienced any dyspeptic symptoms within the last 24 h? (This would include epigastric pain, reflux, flatulence, etc.)		
No		0
Yes	See below	1
1. Severity of Dyspeptic Symptoms		
Mild: aware of it, but not interfering with normal activities		1
Moderate: interfering with some normal activities		2
Severe: interfering with most normal activities		3
2. Did the discomfort disturb your sleep?		
Yes		1
No		0
3. Total duration of dyspeptic symptoms in the past 24 h?		
30 min		1
30-60 min		2
1-6 h		3
6-12 h		4
12-24 h		5
4. Did you take anything for it?		
No		0
Yes		
Nonpharmacological e.g., earlier meal time		1
Pharmacological		2
5. Did you tell anybody about it?		
No		0
Yes		1
Total possible score		12

Table 2. Modifierad version av Glasgow Dyspepsia Questionnaire på Svenska

Symptom registrering		
Har du upplevt några dyspeptiska symptom under de senaste 24 timmarna? (Dyspepsi innebär smärta eller obehag i övre delen av buken, halsbränna, sura uppstötningar, uppspändhet)		
Nej		0
Ja	Fortsätt svara på frågorna nedan	1
1. Svårighetsgraden av dina besvär		
Lätta (jag är medveten om besvären, men stör inte mina normala aktiviteter)		1
Måttliga (stör några av mina normala aktiviteter)		2
Svåra (stör de flesta av mina normala aktiviteter)		3
2. Störde besvären din nattsömn?		
Ja		1
Nej		0
3. Den sammanlagda durationen (tiden) av besvären under de senaste 24 timmarna		
30 min		1
30-60 min		2
1-6 h		3
6-12 h		4
12-24 h		5
4.Tog du något för att lindra besvären?		
Nej		0
Ja- icke-farmalogisk (ex. tidigare måltid)		1
Ja- farmakologisk (dvs. läkemedel)		2
5. Berättade du för någon om dina besvär?		
Nej		0
Ja		1
Total max score		12

Psychological General Well-Being (PGWB) (II) is a generic self-administered instrument to measure subjective well-being or distress (156). The PGWB is well validated and has been used extensively in quality of life studies in both cardiology and gastroenterology (157-159). The PGWB index includes 22 items which are presented in both a global overall score, as well as six dimensions such as anxiety, depressed mood, positive well-being, self-control, general health, and vitality. The questions concern symptoms during the week prior to questionnaire completion. Scores are calculated for each dimension and these are then added together yielding an overall score. The PGWB use a 6-grade Likert scale. The global score range from a maximum value of 132 to a minimum value of 22 where a higher score represents a greater well-being.

Reflux Disease Questionnaire (RDQ) (III) is a 12-item self-administered questionnaire which was designed to assess the frequency and severity of heartburn, acid regurgitation and dyspeptic complaints (pain or burning in the upper stomach) during the week prior to questionnaire completion (160). Symptom frequency and symptom severity are measured on a six-point Likert scale from no occurrence to daily/severe. The 12 questions can be grouped into four symptom dimensions: heartburn, regurgitation, GERD and dyspepsia. The reliability and validity of the RDQ have previously been established in several studies (160, 161)

GERD Impact Scale (GIS) (III) was developed to be a simple tool to monitor how patients respond to treatment of GERD symptoms (162). The GIS questionnaire includes nine items that measure three factors (burning and pain, other acid-related symptoms, and impact of GERD symptoms). Items are scored on a 4-grade scale (never to daily) recording symptoms present during the week prior to questionnaire completion. The GIS scale has recently been validated. Complimentary to the GIS impact scale, patients in study III were asked six accompanying questions (Table 3).

Table 3. Questions asked to patients as a complement to GIS

1. Which is your current treatment? (omeprazole/pantoprazole/esomeprazole/rabeprazole/lanzoprazole/H2 antagonists)
2. What is your normal dosage of your medication? ____ mg
3. How do you take your medicine? (daily, on demand)
4. Do you at any time take higher dose than your doctor recommend? (Always/sometimes/rarely/ never)
5. Despite therapy, have you during the last week of treatment had at least moderate problems with heartburn, acid reflux and/or epigastric pain? (Yes <2/ 2-3 days/ >4/No)
6. Do you find that your acid related symptoms have an influence on your quality of life and your well being? (Yes/No)

Short-Form 36 (SF-36) (III) The Medical Outcome Study Short form 36 (SF-36) is a generic HRQOL instrument, and has been thoroughly tested and validated (163-165). The SF-36 has been widely used in patients with a range of diseases. It measures the health status of the general population, primary care patients, acutely ill patients and chronic disease populations. It consists of 36 items organised into eight domains (physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role limitations caused by emotional problems and mental health) and produces summary physical and mental health measures. The SF-36 is scored from 0 to 100, with a higher score indicating a better HRQOL. The SF-36 has been used in several studies to assess the impact of duodenal ulcer, GERD and reflux esophagitis, and the effect these illnesses may have on HRQOL (100, 166-168).

3. DATA COLLECTION (I, II)

In paper I the following data were collected from the patients medical records: admitting diagnosis, drugs used for GI disorders/symptom, concomitant drug use, information about the acid suppressive therapy i.e. dose and the evaluations for the use of acid suppressive therapy, and where the acid suppressive therapy were started. As a complement to the medical records patients were interviewed if data were unable to be retrieved from the medical records. In paper II the following data were collected from the medical records: age, weight, height,

concomitant diseases other than COPD, drugs used for GI disorders/symptoms, smoking status, and FEV_1readings (data on FEV_1 values were not noted if these were recorded more than six months previously).

4. TEST MEAL (IV)

In study IV, all participants received breakfast after an overnight fast. The test meal consisted of two whole grain sandwiches with a total of 4 slices of cheese, a boiled egg and a glass of milk (200 ml). Blood samples for meal stimulated gastrin were drawn from an indwelling cannula at baseline and at 30 minutes, 45 minutes and 60 minutes after the meal.

5. STUDY MEDICATION (IV)

In paper IV, all participants were randomised in a double-blind fashion to treatment with either pantoprazole 40 mg or visually identical placebo one daily for 28 days. The participants were instructed to take the study medication each morning at breakfast. A reminder telephone call to the participants was made after two weeks of treatment. Tablets were counted after four weeks of treatment.

6. HELICOBACTER PYLORI (IV)

To assess the infection of Helicobacter Pylori the 14 C urea breath test (UBT) was used, Heliprobe (Noster, Sweden) (169). The method is reliable and well validated and is easily performed. The urea breath test has a higher sensitivity compared to the serological test for *H.pylori.*

7. BLOOD SAMPLES (IV)

In paper IV, plasma levels of gastrin and CgA was used as an indirect measurement of the acid inhibition. Gastrin samples were taken prior to meal and at 30, 45 and 60 minutes after the intake of the standard breakfast. The CgA and blood samples were obtained prior to the meal when the volunteers have been fasting over a night. The samples were then centrifuged at 3800 g at $4^{o}C$ for 10 minutes. The plasma and serum were then stored at $-80^{o}C$ until the analysis. Plasma concentrations of gastrin were determined by Immunometric methods with

chemoluminiscence measurements. The CgA concentrations were determined by Radioimmunoassay with reagents from Euro-Diagnostics (Malmö, Sweden). The analysis of gastrin and CgA was performed at the Clinical Central Laboratory at the Sahlgrenska University Hospital.

Blood samples for CYP2C19 status were taken when the volunteers were fasting. Venous blood samples were frozen and stored at -80^{o}C. DNA was isolated according to standard methods. The CYP2C19*2 allele was identified by polymerase chain reaction (PCR) as prescribed by de Moraris et al (170). Similarly the CYP2C19*3 allele was analysed by PCR of exon 4. Analysis was executed with TaqMan assays by Applied Biosystems. Analyses were performed at Genomics core facility, Göteborg, Sweden.

Comments: The gastrin and CgA served as indirect measures of acid inhibition. A more precise way to measure acid inhibition would be to determine acid hypersecretion by aspiration methods. However the invasive nature of measuring aspirations via tubes obviously makes symptom assessments very difficult, if not impossible for the purpose of the study.

8. STATISTICAL METHODS

Results are presented as mean and standard deviation (SD) or standard error of the mean (SEM), and median and interquatile range (IQR). Results in paper II are mostly presented as median and IQR, except when GSRS and PGWB data are compared with the results from the general population, in the latter case, the results (as the original population) are shown as median with 95% confidence interval (CIs) to make comparisons possible. In study IV non-parametric tests were used, but in order to provide more information the numbers and results for dyspeptic symptoms are presented as a mean and standard deviation (SD).

All tests were two-tailed and significance was accepted at the 5% level.

The following statistical methods were used: Student´s *t*-test (II), Mann-Withney *U* test (IV) (Iii), Kruskal-Wallis (III), ANOVA (III), Wilcoxon signed rank test (III), Fisher´s exact test (I, III, IV), Chi squared test (III) and Sperman´s rank correlation for non parametric correlations (IV).

RESULTS

1. USE OF ACID-SUPPRESSIVE THERAPY (I)

A total of 132 (44%) patients among the 301 hospitalised patients received PPIs or H_2-receptor antagonists during the study period. The most frequently used type of medication was PPIs which were used in 126 (95%) of the cases, where as the remaining six (5%) patients received H_2-receptor antagonists.

1.1 Comparison of the usage of acid-suppressive therapy among different wards

On the pulmonary ward 79 (50%) of the patients received AST. On the surgical wards 43 (49%) of the patients received AST, whereas only ten (20%) of the patients on the general internal medicine ward were on AST. A higher proportion of hospitalised patients with pulmonary diseases used AST compared with patients hospitalised on the general internal medicine ward ($p<0.01$). There was no significant difference between pulmonary patients and patients hospitalised on the surgical ward in terms of the proportion of patients receiving AST.

Of the patients receiving AST, 88 (67%) were prescribed AST prior to admission, whereas 44 (33%) began their therapy during the hospitalisation.

1.2 Indications for acid-suppressive therapy

Of the 132 patients receiving AST, 54 (41%) had an adequate indication for the use of AST, whereas 78 patients (59%) lacked an adequate indication. The proportion of patients with inadequate indication for AST was higher among patients hospitalised on the pulmonary ward, compared with the control wards (68 % vs. 47% $p<0.05$).

The most common adequate indication for AST among patients on the pulmonary ward and on the general internal medicine ward was gastroesophageal reflux disease (GERD), which represented the indication in 15 (11%) of the patients (Figure 3), whilst peptic ulcer was the most common adequate indication on the surgical wards.

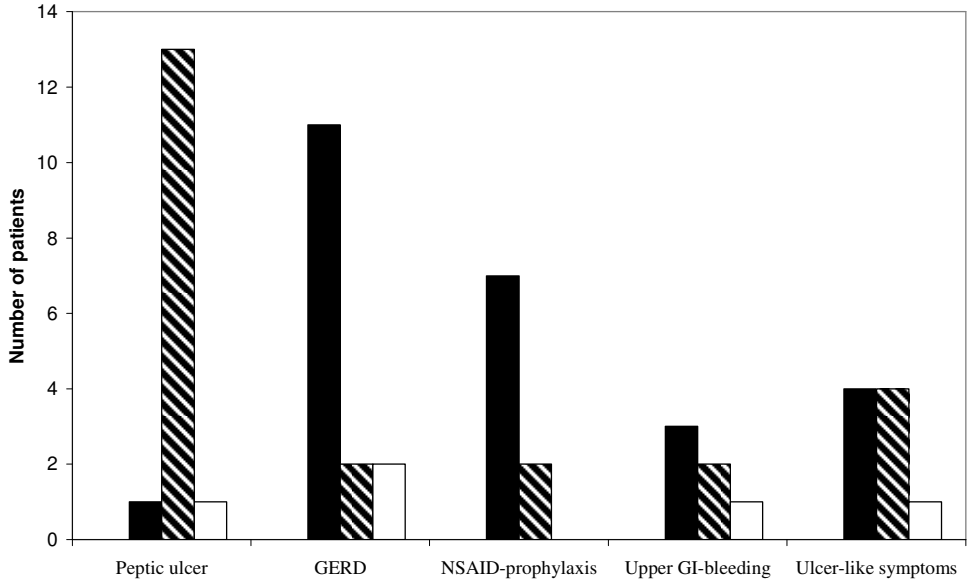

Figure 3. Adequate indications for the use of AST. Black bars represent the pulmonary patients, stripped bars represent the surgical patients and the white bars represent the general medicine patients.

Ulcer prophylaxis during treatment with corticosteroids was the most frequent inadequate use and was observed in 17 (13%) patients. Of these patients, 15 were hospitalised on the pulmonary ward (Figure 4). The most common inadequate indication for AST usage on the other wards was stress ulcer prophylaxis following treatment in the intensive care unit, which was not discontinued when the patients were transferred to general wards, and represented 12 of the cases (Figure 4). There was no significant difference between the distribution of adequate and inadequate indications among patients already taking AST on admission compared to those who commenced AST during hospitalisation (data not shown).

Comments: The decision whether the use of a drug is appropriate varies over time due to new research and new findings. In this study we used the indications approved and listed in the 2002 version of the Swedish National Formulary. Gastrointestinal intestinal haemorrhage prior to endoscopy was also considered an appropriate indication.

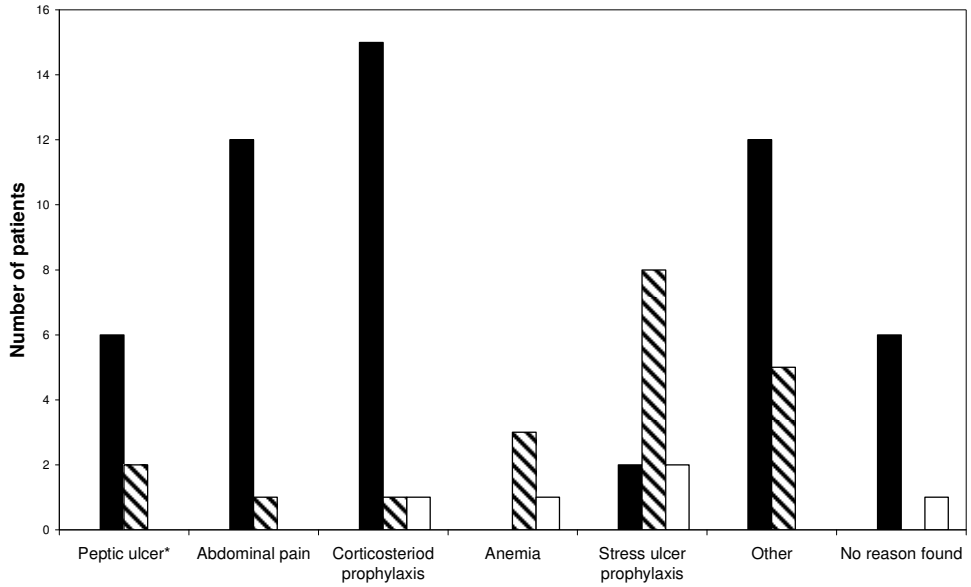

Figure 4. Inadequate indications for the use of AST. Black bars represent the pulmonary patients, stripped bars represent the surgical patients and the white bars represent the general medicine patients.

1. 3 Investigations

Of the 132 patients receiving AST, 56 patients (42%) had undergone gastroscopy. On the pulmonary ward only 25 patients (31%) had been investigated by gastroscopy, compared with the other wards where 31 of 53 patients (58%) had undergone gastroscopy ($p<0.05$). Patients who had undergone gastroscopy were more likely to have an inadequate indication for AST as opposed to patients who had not undergone gastroscopy ($p<0.01$). Of the patients who were on long term treatment for peptic ulcer, none had received HP eradication at any time. Only one patient had undergone 24-hour esophageal pH measurements.

2. GASTROINTESTINAL SYMPTOMS AND HRQOL IN PATIENTS WITH COPD (II)

Patients with COPD had a significantly higher prevalence of gastrointestinal symptoms as compared to the reference values (general population), demonstrated a significantly higher (Table 4). When comparing the COPD group and the CRF group, patients in the COPD group had a tendency to higher GSRS scores, except in the sub-dimension of diarrhoea, but none of these differences reached statistical significance. In all the GSRS domains the score was

significantly higher in both the COPD and the CRF groups compared to the general population (Table 4).

Comments: The fact that the reference values and the values from the CRF patients were taken from another study can be troublesome. There is both gender and age difference among the CRF group and the COPD group compared to the general population. The CRF group and the COPD group were older, and the proportion of females was also higher in this group.

Tabel 4. Comparison of GSRS scores between patients with COPD, patients with CRF and the general population.

	COPD (n=113)	CRF (n=82)	General Population (n=2126)
Total	2.12 (1.92-2.28)***	1.96 (1.81-2.12)***	1.53 (1.50-1.55)
Reflux	1.67 (1.46-1.87)***	1.55 (1.34-1.76)*	1.39 (1.36-1.43)
Abdominal pain	1.93 (1.93-2.16)***	1.80 (1.60-2.00) **	1.56 (1.53-1.59)
Constipation	2.19 (1.89-2.45)***	2.02 (1.73-2.31)***	1.55 (1.51-1.58)
Indigestion	2.47 (2.19-2.70)***	2.10 (1.89-2.31)***	1.78 (1.75-1.82)
Diarrhoea	1.98 (1.76-2.23)***	2.20 (1.86-2.55)***	1.38 (1.35-1.41)

Mean values and 95% confidence interval for the groups. * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$ compared with the general population.

No significant differences were found among COPD patients with a $FEV_1 \leq 50\%$ compared with COPD patients with a $FEV_1 > 50\%$ in any of the GSRS domains. In the COPD group, females had significantly higher GSRS total scores as well as higher reflux scores, abdominal, and indigestion domains compared with males (Figure 5). Among CRF patients no significant effect of gender on GI symptom severity could be detected.

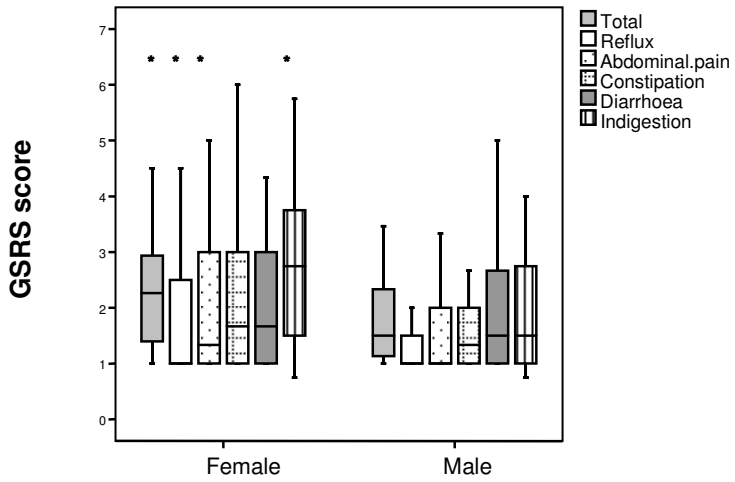

Figure 5. Comparison of the different GSRS domains in females (n=75) and males (n=38) in the COPD patient group. * $P \leq 0.05$. Values are given as medians and interquartile ranges.

The GI symptom severity did not differ significantly between patients receiving theophylline and corticosteroids, and those not receiving these drugs (data not shown). Body mass index had no impact on GI symptoms (data not shown). Sixteen (14%) of the COPD patients fulfilled the Rome II criteria for IBS.

Patients with COPD reported significantly lower scores on all the PGWB dimensions, comparing with both the CRF patients and the general population (Table 5). Body mass index and gender had no impact on the psychological general well being (data not shown). There was no significant difference in any of the PGWB dimensions between the COPD patients with $FEV_1 \leq 50\%$ in comparison with COPD patients having a $FEV_1 > 50\%$ (data not shown).

Out of the 113 COPD patients, 34 (30%) suffered from possible depression as measured by the HAD scale (HAD score of ≥8). Possible anxiety (score of ≥8) was present in 45 (40%) of the COPD population. A negative correlation was found between the GSRS score and the PGWB index, in both COPD patients ($r=-0.49$; $P<0.001$) and CRF patients ($r=-0.43$; $P<0.001$).

Table 5. Comparison of PGWB scores between patients with COPD, patients with CRF and the general population.

	COPD (n=113)	CRF (n=82)	General Population (n=2126)
Totalt	90 (78-104)***	98 (83-113)*	103 (102-104)
Anxiety	23 (20-27)***	25 (22-29)	24 (24-25)
Depressed mood	14 (12-17)***	15 (13-17)	16 (15-16)
Positive well-being	14 (12-16)***	15 (12-18)**	16 (16-17)
Self-controll	14 (12-16)***	15 (14-17)	15 (15-16)
General health	12 (10-14)***	13 (11-16)***	15 (14-15)
Vitality	14 (12-17)***	15 (13-19)***	17 (17-18)

Mean values and 95% confidence interval for the groups. * P≤0.05, ** P≤0.01, ***P≤0.001 compared with the general population.

COPD patients with a high total GSRS score were more likely to have anxiety (measured with HAD) than patients with a low GSRS score ($p<0.0001$). The occurrence of depression (HAD score ≥8) was also associated with a high GSRS score ($p<0.001$).

2.1 Consumption of acid-suppressive therapy among COPD patients

In the COPD group, 30 (26.5%) patients were receiving acid suppressant therapy (AST) were 25 patients (30%) in the CRF group. Among the COPD patients receiving AST, 17 (57%) were also taking corticosteroids orally. Patients with COPD receiving AST reported significantly higher total GSRS scores as well as reflux scores, abdominal pain and indigestion scores compared with those patients without treatment (Table 6).

Table 6. Comparison of GSRS scores between COPD patients using AST and patients not using AST.

	Non users of AST (n=165)	AST users in the COPD group (n=30)
Total	1.60 (1.00-2.00)	2.33 (1.84-2.90) **
Reflux	1.00 (1.00-2.00)	1.50 (1.00-2.50) *
Abdominal pain	1.33 (1.00-2.00)	2.33 (1.17-3.17) ***
Constipation	1.67 (1.00-2.33)	1.67 (1.00-3.33)
Diarrhoea	1.67 (1.00-2.92)	1.33 (1.63-3.50)
Indigestion	1.75 (1.25-2.75)	2.75 (1.84-2.90) **

Values are given as medians and IQR. , * P≤0.05, ** P≤0.01, ***P≤0.001.

AST users also had a significantly lower total PGWB score of 86 (76-101) compared with a PGWB score of 97 (84-111) in those not on AST (P<0.003). All AST users had significantly lower scores in the PGWB domains, than those not using AST except in the dimensions depression and self-control.

3. PATIENTS WITH PERSISTENT SYMPTOMS

A total of 44 (57%) of the 77 patients reported that they had at least moderate problems with heartburn, acid reflux or epigastric pain during at least two or more days over the last week of treatment and all considered that the problems were associated with an impaired quality of life. There were no significant difference between the group of asymptomatic and patients with symptoms, in the domains of age, gender and BMI (data not shown).

3.1 Response to high dose treatment with PPI

Of the 44 patients who originally reported symptoms despite PPI therapy, 18 (41%) were still symptomatic three months later when they completed the same questionnaires and fulfilled the predefined criteria for high dose PPI therapy, being 23% of the original cohort (18/77).

One patient declined treatment due to evaluation of extraintestinal malignancy. Thus, 17 patients were eligible to receive treatment with esomeprazole 40 mg twice daily for a period of four weeks. On this high dose therapy three patients developed diarrhoea during the

treatment and did not want to proceed with this strategy and reverted to their previous treatment. The diarrhoea resolved in all patients. After 12 weeks of treatment, ten patients had no symptoms and tapered down the treatment to the lowest effective PPI dose. The patients had at the end of treatment significantly lower scores on the domains for heartburn, GERD and dyspepsia on the RDQ scale compared with baseline values (Table 7).

Table 7. Change in GI symptoms measured by RDQ for patients treated for 4 to 12 weeks. Before treatment and follow up after 12 weeks.

	Prior to treatment change (n=10)	After 12 weeks (n=10)	change p-value
Heartburn	11.14 (±4.78)	3.29 (±3.30)	0.0313
Regurgitation	6.54 (±4.47)	2.29 (±4.27)	N.S
GERD	18 (±7.62)	5.29 (±6.92)	0.0469
Dyspepsia	7.14 (±4.10)	1.34 (±1.81)	0.0313

After 12 weeks of treatment four out of the seven patients still had persistent symptoms, three patients had no symptoms and tapered down the PPI treatment. The remaining four patients with persistent symptom underwent upper endoscopy. One of the patients was during follow-up diagnosed with microscopic colitis and after successful treatment of her symptoms of diarrhoea with budesonide, the gastrointestinal complaints subsided (no GERD symptoms) and the patient was therefore not a candidate for upper endoscopy. Three patients underwent endoscopy with normal results except for a small hiatal hernia in one patient. There were no signs of esophagitis in any of the patients.

3.2 Quality of life

Quality of life in patients who had at least moderate problems with heartburn, acid reflux or epigastric pain for a period of at least two or more days during the last week of treatment had significantly lower quality of life compared to patients who were satisfied with treatment (data not shown). Patients who tapered-down after 4 or 12 weeks of treatment had

significantly higher quality of life in the dimensions for bodily pain, vitality and physical component after than before treatment as shown in Figure 6.

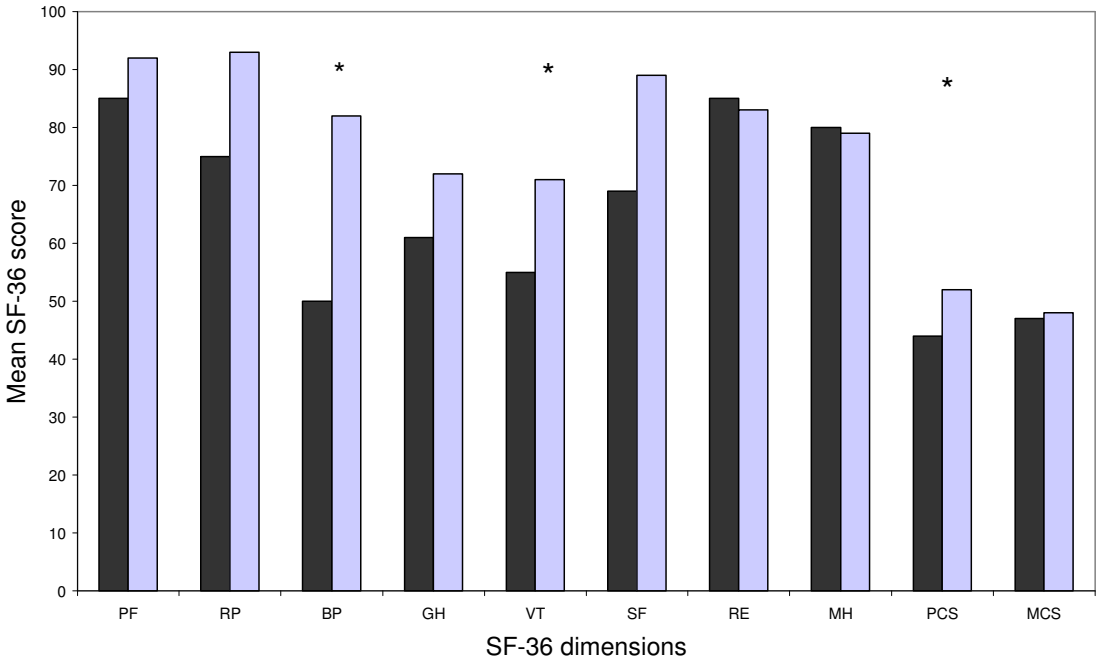

Figure 6. SF-36 dimensions before and after treatment in poor responders. Black bars represents before treatment, and grey bars represent after 4-12 weeks of treatment with high dose PPI.

4. DYSPEPTIC SYMPTOMS AFTER CESSATION OF PPI

The mean aggregated dyspeptic symptoms during the first and the second week after discontinuation of therapy was significantly higher in the pantoprazole group compared with the placebo group ($p<0.05$) (Figure 7). However, no significant difference was observed before or during treatment in the two groups (Figure 7).

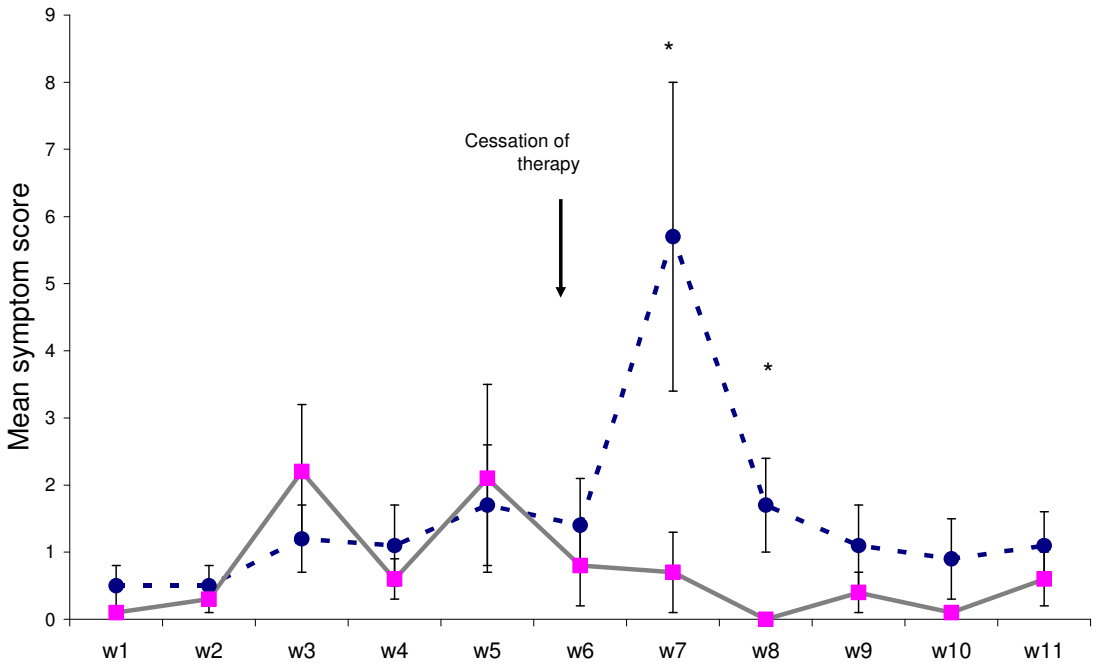

Figure 7. Mean aggregated dyspepsia score, on a weekly basis (mean and SEM) in the pantoprazole group (dotted lines) and in the placebo group (black lines). Weeks 1-2=prior treatment, Weeks 3-6=during treatment, and Weeks 7-12=after treatment. * $p<0.05$

During the first week after treatment, a total of 11 of 25 (44%) volunteers in the pantoprazole group experienced dyspeptic symptoms in contrast to 2 of 23 (9%) of the volunteers in the placebo group ($p=0.009$). During the second week after treatment 6 of 25 (24%) participants in the pantoprazole group experienced dyspeptic symptoms compared to none in the placebo group ($p=0.003$). During the third week in follow-up 4 of 25 (16%) patients in the pantoprazole group had dyspepsia versus 2 of 23 (9%) in the placebo group (NS).

3.2 Gastrin levels

Fasting and meal stimulated gastrin levels measured during the last week of treatment were significantly higher in the pantoprazole group compared to that of the placebo group ($p<0.0001$) (Figure 8). No significant differences were found in the fasting and meal stimulated gastrin levels six weeks after treatment between the pantoprazole group and the placebo group. Nor were there any significant difference found prior to treatment in the fasting gastrin between the pantoprazole group compared with the placebo group. There was however a significant difference between the pantoprazole group and the placebo group in the meal stimulated levels measured 45 min after test meal (Figure 8).

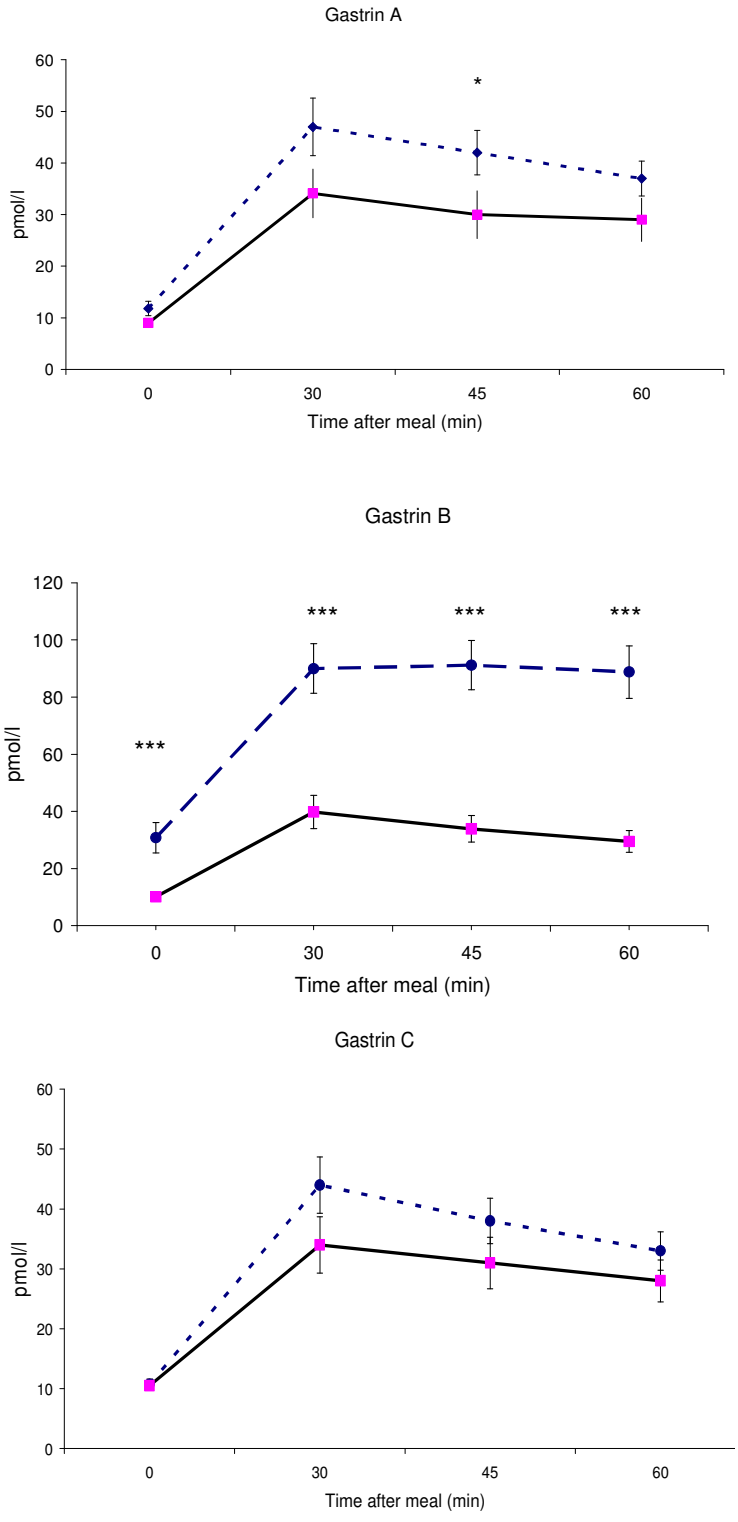

Figure 8. Levels of Gastrin (mean and SEM) in the pantoprazole group (dotted lines) and controls (grey lines). A= Before treatment (1), B= Last week of treatment (2), C= Six weeks after treatment (3). * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

The total dyspeptic symptom scores during the first week after treatment was significantly associated with the basal levels of gastrin ($p<0.01$) (rho=0.477), and the meal stimulated gastrin levels ($p<0.01$) (rho=0.488) at the end of treatment.

3.3 Chromogranin levels

The mean CgA score was similar in the pantoprazole group and the placebo group prior to treatment, as well as six weeks after treatment (N.S) (Figure 9). However the CgA levels were higher in the pantoprazole group (6.1±2.7) compared with the placebo group (3.8±1) during the last week of treatment ($p<0.001$).

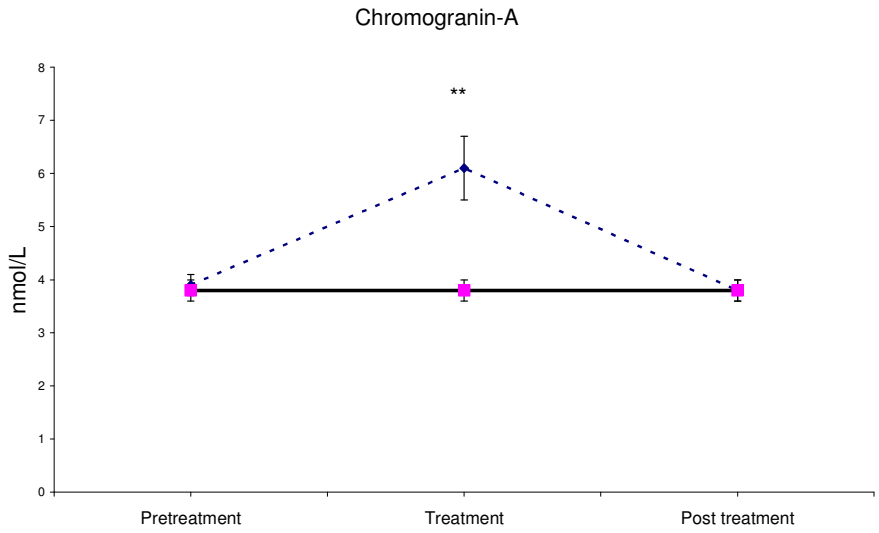

Figure 9. Levels of CgA (mean and SEM) in the pantoprazole group (dotted line) and in the placebo group (black line). Before, during and after treatment. ** $p<0.01$

3.3 CYP2C19 Genotypes

Participants were classified into three groups according to CYP2C19 genotypes. Thirty participants (15 in each treatment group) were homozygous extensive metabolisers (EM) for the wild type allele (wt/wt) and fourteen participants were heterozygous EM, (8 in the pantoprazole group and 6 in the placebo group). Two volunteers (one in each treatment group) were homozygous for the mutated allele (mut/mut) and thus poor metabolisers (PM). Dyspeptic symptoms during the first week after treatment were mainly found among wild type subjects in the pantoprazole group

DISCUSSION

1. USE OF ACID SUPPRESSIVE THERAPY

Hospitalised patients in the current study had a high consumption of acid suppressive drugs with 95% of patients treated with PPIs. Among patients with pulmonary diseases, one in every two patients received treatment with AST, and only 40 % of these patients had an appropriate indication for the treatment. Overuse of acid suppressive therapy has previously been shown in both primary care (82, 91, 171, 172), as well as in hospitalised patients (15, 16, 20, 89, 173, 174). In studies performed to date the range of hospitalised patients receiving AST is 20-54 %. However previous studies addressing indications for AST in hospital settings have only focused on determining the use of AST amongst hospitalised patients in general (15, 16, 89, 173, 174). Information about the use of AST in specific patient groups, with chronic diseases has been limited. A study from our research group has previously shown a high prevalence of AST consumption in patients with another chronic disease, CRF patients (20). In our study a larger proportion of pulmonary patients used AST compared to patients on the internal medicine ward, but not in comparison with patients on the surgical ward.

A significantly larger proportion of the studied pulmonary patients lacked an adequate indication for the use of AST in comparison with patients hospitalised on the surgical and general internal medicine wards in our study. Earlier studies as do recent studies confirm a similarly high level of inadequate use where 61-81% of the prescriptions were not indicated, as determined by consensus review (15, 16, 20, 89, 91). Ulcer prophylaxis during corticosteroid treatment was a common inadequate use among patients on the pulmonary ward. The use of PPIs as ulcer prophylaxis was also a common inadequate indication in hospitalised patients in Italy (89). Oral corticosteroids are among the most widely used drugs in the treatment of patients with pulmonary diseases, especially those with chronic obstructive pulmonary disease (COPD) as was the case in the present study. Previously, use of corticosteroids has been reported to be associated with the development of peptic ulcer, although only in a small minority of patients (76, 77). However it has since been shown that there is no increased risk for peptic ulcer related to corticosteroid use (78, 175). Only those patients on corticosteroids who are concomitantly treated with NSAID are at an increased risk

for peptic ulcer compared with patients taking only corticosteroids (78). Our findings revealed that the ulcer myth still exists and doctors tend to believe that patients with corticosteroids need ulcer protection, although there is no support in evidence for that usage nowadays (78, 175).

The number of patients who received AST and were investigated by upper endoscopy was low, with a large difference between the wards. On the pulmonary ward, only 31% of the patients receiving AST had undergone upper endoscopy, whilst on the other wards the percentage of patients who had undergone upper endoscopy was 58% which was a significantly higher proportion. Our findings are supported by others who found that only a small proportion of patients have undergone upper endoscopy (20, 176), but others have found that a relatively high proportion of patients on AST have undergone upper endoscopy (16). The reason behind the large difference between the proportions of patients that had undergone upper endoscopy was not addressed in the present study, but it is conceivable that patients with pulmonary diseases have a poorer health status making it difficult for these patients to undergo such a procedure. Not all patients receiving PPI as symptomatic treatment of dyspepsia need to undergo upper endoscopy prior to AST. However patients above 50-55 years should undergo upper endoscopy to rule out other serious diseases (12). In the present study most of the pulmonary patients were aged 50 years or above.

Treatment of GERD, was in our study the most common adequate indication in the overall use of AST, which was especially common among patients with pulmonary diseases. A contributing factor to this may be that drugs commonly used by pulmonary patients, such as theophylline, may decrease the pressure of the lower esophageal sphincter (LESP)(177). However, the effect of theophylline on LESP is still controversial (178-180). Theophylline is nowadays not standard treatment for pulmonary patients and it has decreased substantially during the last two decades. The association between GERD and respiratory symptoms is well recognised in the setting of asthma (106-109). In contrast to asthma the prevalence of GERD symptoms is not well established in patients with COPD (110-112).

One explanation for the increasing use of proton pump inhibitors might be the fact that they are effective therapy in many conditions and that the incidence of GERD in the western countries seems to be increasing (181). Proton pump inhibitors also have a preferable safety profile with little interactions and little incidence of adverse effects (52). There is also a lack

of alternative treatment for patients with functional dyspepsia. It has been well documented that PPI are currently prescribed for none approved and sometimes unclear indications (15, 20, 82, 89, 91, 92, 147, 172). In our study a high proportion of patients were prescribed AST for none approved indications, with a relatively high proportion of patients being prescribed AST for abdominal pain. Proton pump inhibitors are today frequently prescribed for non-dyspeptic symptoms in the community, and the prescription is generally continued if a patient is admitted to hospital (147, 182). It has been shown that decisions about AST prescribing do not influence prescription behaviour in primary care (183). The communication between hospital and primary care concerning the background for AST is also insufficient, and this probably influences rational pharmacotherapy.

A number of studies have shown that long term PPI treatment is common (16, 20, 172). In the current study information regarding the duration of treatment was not available in all patients, but in the pulmonary patients the mean treatment time was long (mean 20.3 months). Often patients had been receiving a PPI treatment for a prolonged period of time and neither the primary care physician nor the admitting hospital practitioner had questioned the indication for the continuing use. The use of these drugs needs to be evaluated both in primary care as well as before discharging patients from the hospital the doctor must make sure that the indication is still present.

2. GASTROINTESTINAL SYMPTOMS IN PATIENTS WITH COPD (II)

One of the reasons for undertaking the study on the GI symptoms in patients with COPD was the high frequency of PPI use among these patients as seen in paper I.

In the present study patients with COPD had a high prevalence of GI symptoms in comparison with the general population. However in comparison with patients with another chronic disease (patients with chronic renal failure), no statistical differences in GI symptoms were observed, yet there was a trend toward higher GSRS scores in the COPD group. Previous studies have in line with our results demonstrated a high prevalence of GERD symptoms among COPD patients compared with healthy controls (110, 112) or patients attending an internal medicine clinic (111). The prevalence of GERD in these studies (measured using the Mayo Clinic GER questionnaire) ranged from 15 to 19% (111, 112). Two studies have measured GERD with 24-hour esophageal pH monitoring in patients with severe COPD and found a prevalence of GERD in 57-62 % of patients, but most of these

patients lacked typical GERD symptoms (110, 184). The association between GERD and lower esophageal sphincter (LES) is intuitive, and drugs often used by patients with COPD such as theophylline or anticholinergic drugs have been suggested to lower LESP, but the association has been questioned in other studies as previously mentioned. In the current study there was no association between the use of theophylline and GI symptoms.

Previous studies addressing GERD symptoms in COPD patients and patients with another chronic disease have to date been lacking. Apart from comparison with reference values obtained from the general population in a group of patients with a chronic disease (CRF) served as a control group in our study. A better approach would have been to prospectively recruit control groups. One of the limitations in our study was the use of historical controls.

In the current study COPD patients had a significantly lower total PGWB index of 90 compared with the CRF patients' index of 98 and the general populations' total PGWB index of 102. We found an association between a high total GSRS score and depression and anxiety. Furthermore, a negative correlation between GSRS score and PGWB index was also found to be present. These findings imply that GI symptoms may have a clinically meaningful impact on quality of life for COPD patients. Previous studies have shown that the presence of upper GI symptoms has a negative impact on well-being and other aspects of quality of life in individuals consulting health care (185).

The use of acid-suppressant drugs was found in 26.5% of the patients with COPD. As shown in paper I there was a high consumption of acid suppressant drugs among patients with pulmonary diseases. Interestingly, patients receiving acid suppressant medication had a significantly higher total GSRS score, and higher scores for the reflux, abdominal pain and indigestion dimensions, than those patients not receiving acid suppressant drugs. The reason for this is unclear. A possible explanation may be insufficient treatment of GERD with an inadequately low dose of AST or the fact that, their GI symptoms are not acid-related. Another possibility may also be non-compliance with their medication. However, the increased GI symptomatology in these patients requires diagnostic work-up in these patients in order to explore different treatment options that aim for a better treatment for GI symptoms and hopefully a better psychological well-being.

3. TREATMENT OF PATIENTS REFRACTORY TO STANDARD TREATMENT

In the initial assessment of quality of GERD therapy a significant proportion of GERD patients treated with PPI had persistent symptoms in spite of therapy. However, despite seemingly persistent symptoms a very small proportion of patients do not respond to high dose PPI therapy for a period of at least four weeks and up to three months. Only a small proportion of patients had persistent symptoms after high dose PPI treatment. Of the patients without significant symptomatic improvement after high dose therapy the dominant symptoms were not those of GERD.

Like our study, others have shown that a significant proportion of GERD patients are refractory to treatment with PPI (186, 187). The proportion of patients with GERD persistent symptoms in spite of standard dose PPI therapy range from 20 to 40 %. However the definition of "poor response" to PPIs or persistent symptoms despite therapy is controversial (26, 27, 125). Heartburn not adequately relieved after four weeks of therapy with a standard PPI dose has been defined as "refractory"(26). The true number of PPI-refractory patients has been considered to be overestimated (125). It is of major importance to treat these patients both sufficiently in time and dose before symptoms can be called refractory. The number of responders has been found to increase for up to eight to 12 weeks of acid suppressive treatment (188, 189). The results of the current study are in line with this as a significant proportion of patients had symptomatic improvement or PPI response after 12 weeks of treatment. The proper therapeutic approach to patients who fail standard-dose PPI once daily is not well established in the literature (26). Clinical guidelines have supported increasing the dose to twice daily ("double-dose") in these patients. Studies evaluating alternative PPI treatment with a double dose have shown benefit with a higher PPI dose (double dose) (26, 190). Doubling the PPI is also suggested to be beneficial in patients with functional heartburn (191). In the current study participants received 40 mg esomeprazole twice daily, which is a doubling of the dose used in the most previous studies where patients responded poorly to standard PPI dose. This dose was arbitrarily chosen. However we hypothesized that this dose would eliminate acid reflux in the vast majority of patients. Ph monitoring studies have revealed that 31% of patients taking standard dose PPI had elevated acid exposure, as opposed to only 4 % of patients having an elevated acid exposure on a twice-daily PPI dose (192). In our study patients were treated for at least one month up to three months with high dose PPI.

It is seemingly important to use a high PPI dose for a sufficiently long–treatment period in order to receive optimal response especially in patients with oesophageal hypersensitivity (126).

Assessment of the response to therapy is of major importance in the management of most clinical conditions but in GERD objective instruments to assess and monitor response to therapy have been largely lacking. Information on the symptomatology of GERD patients has been shown to be more reliable with the help of a structured questionnaire than symptoms reported at the initial doctor consultation. Recently the GIS questionnaire, as used in the current study designed to monitor response to GERD therapy was validated (192). Poor agreement between GERD patients and clinicians in their assessment of symptom severity has been demonstrated, with physicians tending to underestimate symptom severity and overestimate the treatment effects (193). The initial assessment of symptom severity in GERD patients on PPI therapy in the current study revealed that more than half of the patients seemed to have suboptimal response to therapy. Thus, increased use of symptom based questionnaires such as the GIS questionnaire in clinical practice may identify patients with suboptimal GERD treatment. Evaluation of symptom is of importance during treatment, especially since many patients are on long term treatment in order to optimize therapy.

In the current study we also wanted to determine the natural history of patients who were symptomatic despite PPI therapy. Our results indicate that this is a heterogeneous group as 33% of the initial "poor responders" were satisfied with the same GERD therapy during the three following months after initial assessment. Thus, a cross-sectional survey can be misleading as some patients experience spontaneous remission. The explanation of this is unclear but it can not be excluded that the survey or participation in a clinical study may provide part of the explanation.

Poor compliance is probably a common cause of a seemingly PPI failure and may be the single most common cause of persistent symptoms when these symptoms do not resolve after commencement of PPI therapy (194). In patients with refractory GERD symptoms the initial step for doctors should be to ask patients about the way in which they take their PPI, in particular the dose, timing and frequency of dosing. In our study patients were told to take the PPI 30 minutes prior to both breakfast and dinner, as the timing of the dose can be critical for maximal effect. Proton pump inhibitors are often taken inappropriately and this was revealed

in a US survey showing that only 27% of GERD patients dose their PPI correctly (i.e. up to 60 minutes before any meal of the day). Out of these patients only 9.6% consumed their PPI optimally (i.e. 15-60 minutes before the first meal of the day) (195). Further in a study among primary care physicians across the USA, only 36 % of doctors gave their patients advice on how to take their medication (196). A large population-based study revealed that only 55% of GERD patients take their PPI as prescribed by the doctor (197). One explanation for this high non-compliance is complete resolution of symptoms early on in the treatment. In this study we were not able to assess compliance but as most patients were satisfied with their treatment at the end of the study period, it is unlikely that compliance was poor in our patients during the study period.

4. DYSPEPTIC SYMPTOM DEVELOPMENT (IV)

It has previously been proposed that withdrawal of PPI produces rebound hypersecretion of gastric acid (22-24). However the clinical significance of the proposed rebound of acid is uncertain and its existence have been questioned in a recent review (25). The current study demonstrated that treatment with pantoprazole 40 mg per day for four week course seems to induce dyspeptic symptoms in previously healthy asymptomatic subjects. Upper GI symptoms were significantly more frequent in the pantoprazole group during the first two weeks after cessation of PPI therapy than after cessation of placebo. A total of 44% of subjects in the pantoprazole group experienced upper GI symptoms during the first week after cessation compared with 9% in the placebo group. In agreement with the study by Smith et al. comparing H_2-receptor antagonist with placebo we found that previously asymptomatic healthy volunteers developed upper GI symptoms after cessation of PPI (148). Proton pump inhibitors have a longer lasting acid suppressive effect after cessation due to irreversible inhibition of the proton pump, and it takes a number of days after treatment for newly synthesized proton pumps to generate full effect. As shown in the current study the symptoms were present during the first week following cessation and also after the second week. The symptom development during the first week following cessation was most frequent at day five and six in our study.

Our results extend the current understanding as do the study by Smith et al., were no measurements of gastrin and CgA were performed (148). Furthermore, as shown in our study the CgA levels were significantly increased during the last day of treatment in the pantoprazole group compared with baseline values. Several studies have suggested that serum CgA levels can be used as a test to evaluate ECL-cell hyperplasia in patients using acid suppressive therapy (24, 198-200). Our findings suggest that the participants in the pantoprazole group showed development of ECL-cell hyperplasia which is suggested by significantly higher CgA levels. However six weeks after treatment the CgA and gastrin values were normalized, showing a rapid recovery to normal gastrin function. This may be related to the relatively short period of treatment. On the other hand studies evaluating treatment with PPI for a longer period of time (4-12 months) have demonstrated rebound acid hypersecretion lasting for at least 8 weeks, but no more than 26 weeks (21, 22, 137).

In agreement with other studies fasting gastrin as well as gastrin levels after meal intake were significantly increased on the last day of treatment compared with baseline values in the pantoprazole group in the present study (22-24). A significant association between the degree of increase in maximal and fasting plasma gastrin has been proposed to be of importance for acid rebound hypersecretion (22). Gillen et al. have demonstrated that the degree of rebound hypersecretion is related to the elevation of plasma gastrin during treatment. In the present study we found a correlation between the development of dyspeptic symptoms and fasting as well as meal stimulated gastrin levels. A recent study demonstrated that GERD patients with high fasting gastrin had more difficulties discontinuing PPI than patients with low fasting gastrin (201). The results of the current study suggest that the degree of acid inhibition is of importance for GI symptom development after the withdrawal of PPIs.

Some studies have failed to show acid rebound hypersecretion after cessation of a PPI, but in these studies has not determined *H. pylori* status in the participants (136-139). The results from the studies showing the presence of acid hypersecretion post PPI treatment have been questioned for being non-blinded and for other methodological limitations such as small study populations (22-24). However, our results with a double-blind, parallel group design clearly demonstrates that acid rebound hypersecretion exists and that it is clinically relevant. Another strength in our study is the relatively large sample size compared to previous studies (23, 24, 202).

A substantial proportion of patients that are prescribed PPI for an extended period have indications that do not require long-term PPI treatment (203). It is conceivable that long-term treatment with PPIs might induce exacerbation of symptoms after treatment discontinuation, which can lead to the need for continuing treatment, therefore creating a problem which was not there from the beginning. The results from our study suggest that that may partly be the problem in long-term treatment. Knowledge regarding the occurrence of acid rebound hypersecretion after treatment with PPI is of importance both for patients as well as for doctor when discontinuing treatment. The dyspepsia we found may resolve spontaneously within two weeks. Therefore doctors should be discouraged from recommending treatment if symptoms occur immediately after cessation. However a study of the occurrence of symptomatic acid rebound hypersecretion in patients has not yet been undertaken and our results need to be confirmed in patients with conditions that require PPI treatment.

In conclusion, we have demonstrated that after a short course of PPI development of significant dyspepsia appears in previously asymptomatic healthy volunteers in the first and second week after treatment cessation.

SUMMARY AND CONCLUSION

1. The use of acid suppressive therapy in hospitalised patients was common and patients with pulmonary disease had particularly consumption of proton pump inhibitors. A large proportion of patients with pulmonary disease that receive acid-suppressive drugs have an inadequate indication for the use. The most frequent inadequate indication among these patients was ulcer prophylaxis during corticosteroid treatment.

2. Patients with COPD had a high prevalence of gastrointestinal symptoms in comparison with the general population, but not in comparison with patients with another chronic disease. The gastrointestinal symptoms in patients with COPD were associated with impaired psychological well-being, indicating that GI symptoms might have a clinically meaningful impact on quality of life for COPD patients.

3. A relatively large proportion of GERD patients have persistent symptoms in spite of therapy with PPI. High dose treatment with PPI for 4 to 12 weeks was associated with improvement in GERD symptoms in the vast majority of patients.

4. Healthy volunteers randomised to a short course of a PPI (pantoprazole) developed significant dyspeptic symptoms in comparison with those receiving placebo after cessation. These dyspeptic symptoms were present for at least two weeks. Upper GI symptoms score correlates to basal as well as meal stimulated gastrin levels at end of treatment.

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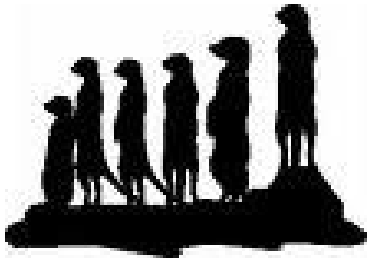

REFERENCES

1. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut. 2005; 54 :710-7.
2. Diaz-Rubio M, Moreno-Elola-Olaso C, Rey E, Locke GR, 3rd, Rodriguez-Artalejo F. Symptoms of gastro-oesophageal reflux: prevalence, severity, duration and associated factors in a Spanish population. Aliment Pharmacol Ther. 2004; 19:95-105.
3. El-Serag HB, Petersen NJ, Carter J, Graham DY, Richardson P, Genta RM, et al. Gastroesophageal reflux among different racial groups in the United States. Gastroenterology. 2004; 126:1692-9.
4. Kennedy T, Jones R. The prevalence of gastro-oesophageal reflux symptoms in a UK population and the consultation behaviour of patients with these symptoms. Aliment Pharmacol Ther. 2000; 14:1589-94.
5. Locke GR, 3rd, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ, 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology. 1997; 112:1448-56.
6. Shaheen N, Provenzale D. The epidemiology of gastroesophageal reflux disease. Am J Med Sci. 2003; 326:264-73.
7. Talley NJ. Review article: gastro-oesophageal reflux disease -- how wide is its span? Aliment Pharmacol Ther. 2004; 20 Suppl 5:27-37.
8. Agreus L, Svardsudd K, Nyren O, Tibblin G. The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population. A report from the Abdominal Symptom Study. Scand J Gastroenterol. 1994; 29:102-9.
9. Jones RH, Lydeard SE, Hobbs FD, Kenkre JE, Williams EI, Jones SJ, et al. Dyspepsia in England and Scotland. Gut. 1990; 31:401-5.
10. Kay L, Jorgensen T. Epidemiology of upper dyspepsia in a random population. Prevalence, incidence, natural history, and risk factors. Scand J Gastroenterol. 1994 ;29:2-6.
11. Talley NJ, Zinsmeister AR, Schleck CD, Melton LJ, 3rd. Dyspepsia and dyspepsia subgroups: a population-based study. Gastroenterology. 1992;102(4 Pt 1):1259-68.
12. Talley NJ, Silverstein MD, Agreus L, Nyren O, Sonnenberg A, Holtmann G. AGA technical review: evaluation of dyspepsia. American Gastroenterological Association. Gastroenterology. 1998; 114:582-95.
13. Scarpignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Dig Dis. 2006; 24:11-46.
14. Gullotta R, Ferraris L, Cortelezzi C, Minoli G, Prada A, Comin U, et al. Are we correctly using the inhibitors of gastric acid secretion and cytoprotective drugs? Results of a multicentre study. Ital J Gastroenterol Hepatol. 1997; 29:325-9.
15. Nardino RJ, Vender RJ, Herbert PN. Overuse of acid-suppressive therapy in hospitalized patients. Am J Gastroenterol. 2000; 95:3118-22.
16. Naunton M, Peterson GM, Bleasel MD. Overuse of proton pump inhibitors. J Clin Pharm Ther. 2000; 25:333-40.
17. Touborg-Lassen. Acid-related disorders and use of antisecretory medication. Dan Med Bull. 2007; 54:18-30.
18. Guillemot F, Ducrotte P, Bueno L. Prevalence of functional gastrointestinal disorders in a population of subjects consulting for gastroesophageal reflux disease in general practice. Gastroenterol Clin Biol. 2005; 29:243-6.

19. Ronkainen J, Aro P, Storskrubb T, Johansson SE, Lind T, Bolling-Sternevald E, et al. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. Scand J Gastroenterol. 2005; 40:275-85.
20. Strid H, Simren M, Bjornsson ES. Overuse of acid suppressant drugs in patients with chronic renal failure. Nephrol Dial Transplant. 2003; 18:570-5.
21. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. Aliment Pharmacol Ther. 2005; 21:149-54.
22. Gillen D, Wirz AA, Ardill JE, McColl KE. Rebound hypersecretion after omeprazole and its relation to on-treatment acid suppression and Helicobacter pylori status. Gastroenterology. 1999; 116:239-47.
23. Gillen D, Wirz AA, McColl KE. Helicobacter pylori eradication releases prolonged increased acid secretion following omeprazole treatment. Gastroenterology. 2004; 126:980-8.
24. Waldum HL, Arnestad JS, Brenna E, Eide I, Syversen U, Sandvik AK. Marked increase in gastric acid secretory capacity after omeprazole treatment. Gut. 1996; 39:649-53.
25. Hunfeld NG, Geus WP, Kuipers EJ. Systematic review: Rebound acid hypersecretion after therapy with proton pump inhibitors. Aliment Pharmacol Ther. 2007; 25:39-46.
26. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next? Aliment Pharmacol Ther. 2005; 22:79-94.
27. Sgouros SN, Mantides A. Refractory heartburn to proton pump inhibitors: epidemiology, etiology and management. Digestion. 2006; 73:218-27.
28. Wolfe MM, Soll AH. The physiology of gastric acid secretion. N Engl J Med. 1988; 319:1707-15.
29. Hersey SJ, Sachs G. Gastric acid secretion. Physiol Rev. 1995 Jan;75(1):155-89.
30. Glynn IM, Karlish SJ. Occluded cations in active transport. Annu Rev Biochem. 1990; 59:171-205.
31. Sachs G. Proton pump inhibitors and acid-related diseases. Pharmacotherapy. 1997; 17:22-37.
32. Waldum HL, Brenna E, Kleveland PM, Sandvik AK, Syversen U. Review article: the use of gastric acid-inhibitory drugs--physiological and pathophysiological considerations. Aliment Pharmacol Ther. 1993; 7:589-96.
33. Malfertheiner P, Fass R, Quigley EM, Modlin IM, Malagelada JR, Moss SF, et al. Review article: from gastrin to gastro-oesophageal reflux disease--a century of acid suppression. Aliment Pharmacol Ther. 2006; 23:683-90.
34. Black JW, Duncan WA, Durant CJ, Ganellin CR, Parsons EM. Definition and antagonism of histamine H 2 -receptors. Nature. 1972; 236:385-90.
35. Garner A, Fadlallah H, Parsons ME. 1976 and all that!--20 years of antisecretory therapy. Gut. 1996; 39:784-6.
36. Fellenius E, Berglindh T, Sachs G, Olbe L, Elander B, Sjostrand SE, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H+ + K+)ATPase. Nature. 1981; 290:159-61.
37. Paimela H, Oksala NK, Kivilaakso E. Surgery for peptic ulcer today. A study on the incidence, methods and mortality in surgery for peptic ulcer in Finland between 1987 and 1999. Dig Surg. 2004; 21:185-91.
38. Gledhill T, Howard OM, Buck M, Paul A, Hunt RH. Single nocturnal dose of an H2 receptor antagonist for the treatment of duodenal ulcer. Gut. 1983; 24:904-8.

39. Nwokolo CU, Smith JT, Gavey C, Sawyerr A, Pounder RE. Tolerance during 29 days of conventional dosing with cimetidine, nizatidine, famotidine or ranitidine. Aliment Pharmacol Ther. 1990; 4 Suppl 1:29-45.
40. Hatlebakk JG, Katz PO, Camacho-Lobato L, Castell DO. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. Aliment Pharmacol Ther. 2000; 14:1267-72.
41. Wolfe MM, Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer , gastroesophageal reflux disease, and stress-related erosive syndrome. Gastroenterology. 2000; 118(2 Suppl 1):S9-31.
42. Stedman CA, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. Aliment Pharmacol Ther. 2000; 14:963-78.
43. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet. 1996; 31:9-28.
44. Meyer UA. Interaction of proton pump inhibitors with cytochromes P450: consequences for drug interactions. Yale J Biol Med. 1996; 69:203-9.
45. Tucker GT. The interaction of proton pump inhibitors with cytochromes P450. Aliment Pharmacol Ther. 1994; 8 Suppl 1:33-8.
46. Andersson T, Miners JO, Veronese ME, Tassaneeyakul W, Meyer UA, Birkett DJ. Identification of human liver cytochrome P450 isoforms mediating omeprazole metabolism. Br J Clin Pharmacol. 1993; 36:521-30.
47. Huber R, Kohl B, Sachs G, Senn-Bilfinger J, Simon WA, Sturm E. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. Aliment Pharmacol Ther. 1995; 9:363-78.
48. Kromer W, Postius S, Riedel R, Simon WA, Hanauer G, Brand U, et al. BY 1023/SK&F 96022 INN pantoprazole, a novel gastric proton pump inhibitor, potently inhibits acid secretion but lacks relevant cytochrome P450 interactions. J Pharmacol Exp Ther. 1990;254:129-35.
49. Simon WA, Budingen C, Fahr S, Kinder B, Koske M. The H+, K(+)-ATPase inhibitor (BY1023/SK&F96022) interacts less with cytochrome P450 than omeprazole and lansoprazole. Biochem Pharmacol. 1991; 42:347-55.
50. Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. Pharmacogenomics. 2004; 5:181-202.
51. Sagar M, Tybring G, Dahl ML, Bertilsson L, Seensalu R. Effects of omeprazole on intragastric pH and plasma gastrin are dependent on the CYP2C19 polymorphism. Gastroenterology. 2000; 119:670-6.
52. Richardson P, Hawkey CJ, Stack WA. Proton pump inhibitors. Pharmacology and rationale for use in gastrointestinal disorders. Drugs. 1998; 56:307-35.
53. Burget DW, Chiverton SG, Hunt RH. Is there an optimal degree of acid suppression for healing of duodenal ulcers? A model of the relationship between ulcer healing and acid suppression. Gastroenterology. 1990; 99:345-51.
54. Sachs G, Shin JM, Munson K, Vagin O, Lambrecht N, Scott DR, et al. Review article: the control of gastric acid and Helicobacter pylori eradication. Aliment Pharmacol Ther. 2000; 14:1383-401.
55. Huang JQ, Hunt RH. pH, healing rate and symptom relief in acid-related diseases. Yale J Biol Med. 1996; 69:159-74.
56. Duplessis DJ. Pathogenesis of Gastric Ulceration. Lancet. 1965; 1:974-8.
57. Bonagura AF, Dabezies MA. Helicobacter pylori infection. The importance of eradication in patients with gastric disease. Postgrad Med. 1996; 100:115-6.

58. Malfertheiner P, Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, et al. Current concepts in the management of Helicobacter pylori infection--the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther. 2002; 16:167-80.
59. Schoen RT, Vender RJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage. Am J Med. 1989; 86:449-58.
60. Butt JH, Barthel JS, Moore RA. Clinical spectrum of the upper gastrointestinal effects of nonsteroidal anti-inflammatory drugs. Natural history, symptomatology, and significance. Am J Med. 1988; 84:5-14.
61. Ekstrom P, Carling L, Wetterhus S, Wingren PE, Anker-Hansen O, Lundegardh G, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous non-steroidal anti-inflammatory drug therapy. A Nordic multicentre study. Scand J Gastroenterol. 1996; 31:753-8.
62. McCarthy DM. Prevention and treatment of gastrointestinal symptoms and complications due to NSAIDs. Best Pract Res Clin Gastroenterol. 2001; 15:755-73.
63. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, Helicobacter pylori, and smoking. J Clin Gastroenterol. 1997; 24:2-17.
64. Kahrilas PJ. Gastroesophageal reflux disease. JAMA. 1996; 276:983-8.
65. Modlin IM, Moss SF, Kidd M, Lye KD. Gastroesophageal reflux disease: then and now. J Clin Gastroenterol. 2004;38:390-402.
66. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900-20.
67. Lambert R. Review article: current practice and future perspectives in the management of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 1997; 11:651-62.
68. Jones R, Bytzer P. Review article: acid suppression in the management of gastro-oesophageal reflux disease--an appraisal of treatment options in primary care. Aliment Pharmacol Ther. 2001; 15:765-72.
69. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. The Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 1999; 94:1434-42.
70. Talley NJ, Meineche-Schmidt V, Pare P, Duckworth M, Raisanen P, Pap A, et al. Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). Aliment Pharmacol Ther. 1998; 12:1055-65.
71. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev. 2006(4):CD001960.
72. Agreus L, Svardsudd K, Talley NJ, Jones MP, Tibblin G. Natural history of gastroesophageal reflux disease and functional abdominal disorders: a population-based study. Am J Gastroenterol. 2001; 96:2905-14.
73. Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ, 3rd. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. Am J Epidemiol. 1992 ;136:165-77.
74. Thompson WG. Placebos: a review of the placebo response. Am J Gastroenterol. 2000; 95:1637-43.
75. Wong WM, Wong BC, Hung WK, Yee YK, Yip AW, Szeto ML, et al. Double blind, randomised, placebo controlled study of four weeks of lansoprazole for the treatment of functional dyspepsia in Chinese patients. Gut. 2002; 51:502-6.

76. Messer J, Reitman D, Sacks HS, Smith H, Jr., Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med. 1983; 309:21-4.
77. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med. 1976; 294:473-9.
78. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med. 1991; 114:735-40.
79. ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998. Am J Health Syst Pharm. 1999; 56:347-79.
80. Howden CW. Use of proton-pump inhibitors in complicated ulcer disease and upper gastrointestinal tract bleeding. Am J Health Syst Pharm. 1999;56 (23 Suppl 4):S5-11.
81. Raynard B, Nitenberg G. [Is prevention of upper digestive system hemorrhage in intensive care necessary?]. Schweiz Med Wochenschr. 1999; 129:1605-12.
82. Bashford JN, Norwood J, Chapman SR. Why are patients prescribed proton pump inhibitors? Retrospective analysis of link between morbidity and prescribing in the General Practice Research Database. Bmj. 1998; 317:452-6.
83. Marshall JK, Grootendorst PV, O'Brien BJ, Dolovich LR, Holbrook AM, Levy AR. Impact of reference-based pricing for histamine-2 receptor antagonists and restricted access for proton pump inhibitors in British Columbia. CMAJ. 2002; 166:1655-62.
84. Martin RM, Lim AG, Kerry SM, Hilton SR. Trends in prescribing H2-receptor antagonists and proton pump inhibitors in primary care. Aliment Pharmacol Ther. 1998; 12:797-805.
85. McManus P, Marley J, Birkett DJ, Lindner J. Compliance with restrictions on the subsidized use of proton pump inhibitors in Australia. Br J Clin Pharmacol. 1998; 46:409-11.
86. Westbrook JI, Duggan AE, McIntosh JH. Prescriptions for antiulcer drugs in Australia: volume, trends, and costs. BMJ. 2001; 323:1338-9.
87. Koop H, Arnold R. Long-term maintenance treatment of reflux esophagitis with omeprazole. Prospective study in patients with H2-blocker-resistant esophagitis. Dig Dis Sci. 1991; 36:552-7.
88. Zeitoun P, Rampal P, Barbier P, Isal JP, Eriksson S, Carlsson R. [Omeprazole (20 mg daily) compared to ranitidine (150 mg twice daily) in the treatment of esophagitis caused by reflux. Results of a double-blind randomized multicenter trial in France and Belgium]. Gastroenterol Clin Biol. 1989; 13:457-62.
89. Scagliarini R, Magnani E, Pratico A, Bocchini R, Sambo P, Pazzi P. Inadequate use of acid-suppressive therapy in hospitalized patients and its implications for general practice. Dig Dis Sci. 2005; 50:2307-11.
90. Boutet R, Wilcock M, MacKenzie I. Survey on repeat prescribing for acid suppression drugs in primary care in Cornwall and the Isles of Scilly. Aliment Pharmacol Ther. 1999;13:813-7.
91. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. Postgrad Med J. 2007; 83:66-8.
92. Pillans PI, Kubler PA, Radford JM, Overland V. Concordance between use of proton pump inhibitors and prescribing guidelines. Med J Aust. 2000; 172:16-8.
93. Bergner M. Quality of life, health status, and clinical research. Med Care. 1989; 27(3 Suppl):S148-56.
94. Moyer CA, Fendrick AM. Measuring health-related quality of life in patients with upper gastrointestinal disease. Dig Dis. 1998; 16:315-24.

95. Wiklund I. Review of the quality of life and burden of illness in gastroesophageal reflux disease. Dig Dis. 2004;22:108-14.
96. Kulig M, Leodolter A, Vieth M, Schulte E, Jaspersen D, Labenz J, et al. Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease-- an analysis based on the ProGERD initiative. Aliment Pharmacol Ther. 200; 18:767-76.
97. Enck P, Dubois D, Marquis P. Quality of life in patients with upper gastrointestinal symptoms: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol Suppl. 1999;231:48-54.
98. Frank L, Kleinman L, Ganoczy D, McQuaid K, Sloan S, Eggleston A, et al. Upper gastrointestinal symptoms in North America: prevalence and relationship to healthcare utilization and quality of life. Dig Dis Sci. 2000; 45:809-18.
99. Koloski NA, Talley NJ, Boyce PM. The impact of functional gastrointestinal disorders on quality of life. Am J Gastroenterol. 2000; 95:67-71.
100. Revicki DA, Sorensen S, Maton PN, Orlando RC. Health-related quality of life outcomes of omeprazole versus ranitidine in poorly responsive symptomatic gastroesophageal reflux disease. Dig Dis. 1998; 16:284-91.
101. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004;364:613-20.
102. Lundback B, Gulsvik A, Albers M, Bakke P, Ronmark E, van den Boom G, et al. Epidemiological aspects and early detection of chronic obstructive airway diseases in the elderly. Eur Respir J Suppl. 2003 May;40:3s-9s.
103. Lindstrom M, Jonsson E, Larsson K, Lundback B. Underdiagnosis of chronic obstructive pulmonary disease in Northern Sweden. Int J Tuberc Lung Dis. 2002; 6:76-84.
104. Mokhlesi B. Clinical implications of gastroesophageal reflux disease and swallowing dysfunction in COPD. Am J Respir Med. 2003; 2:117-21.
105. Crowell MD, Zayat EN, Lacy BE, Schettler-Duncan A, Liu MC. The effects of an inhaled beta(2)-adrenergic agonist on lower esophageal function: a dose-response study. Chest. 2001; 120:1184-9.
106. Compte L, Garrigues V, Perpina M, Ponce J. Prevalence of gastroesophageal reflux in asthma. J Asthma. 2000; 37:175-82.
107. Field SK, Underwood M, Brant R, Cowie RL. Prevalence of gastroesophageal reflux symptoms in asthma. Chest. 1996; 109:316-22.
108. Harding SM, Guzzo MR, Richter JE. 24-h esophageal pH testing in asthmatics: respiratory symptom correlation with esophageal acid events. Chest. 1999; 115:654-9.
109. Sontag SJ, Schnell TG, Miller TQ, Khandelwal S, O'Connell S, Chejfec G, et al. Prevalence of oesophagitis in asthmatics. Gut. 1992; 33:872-6.
110. Casanova C, Baudet JS, del Valle Velasco M, Martin JM, Aguirre-Jaime A, de Torres JP, et al. Increased gastro-oesophageal reflux disease in patients with severe COPD. Eur Respir J. 2004; 23:841-5.
111. Mokhlesi B, Morris AL, Huang CF, Curcio AJ, Barrett TA, Kamp DW. Increased prevalence of gastroesophageal reflux symptoms in patients with COPD. Chest. 2001; 119:1043-8.
112. Phulpoto MA, Qayyum S, Rizvi N, Khuhawar SM. Proportion of gastroesophageal reflux symptoms in patients with chronic obstructive pulmonary disease. J Pak Med Assoc. 2005; 55:276-9.
113. Rascon-Aguilar IE, Pamer M, Wludyka P, Cury J, Coultas D, Lambiase LR, et al. Role of gastroesophageal reflux symptoms in exacerbations of COPD. Chest. 2006; 130:1096-101.

114. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA. 2004; 292:1955-60.
115. Laheij RJ, Van Ijzendoorn MC, Janssen MJ, Jansen JB. Gastric acid-suppressive therapy and community-acquired respiratory infections. Aliment Pharmacol Ther. 2003; 18:847-51.
116. Cunningham R, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. J Hosp Infect. 2003; 54:243-5.
117. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA. 2005; 294:2989-95.
118. Yearsley KA, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. Aliment Pharmacol Ther. 2006; 24:613-9.
119. Neal KR, Scott HM, Slack RC, Logan RF. Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. BMJ. 1996; 312:414-5.
120. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006; 296:2947-53.
121. Bardhan KD. The role of proton pump inhibitors in the treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 1995; 9 Suppl 1:15-25.
122. Havelund T, Lind T, Wiklund I, Glise H, Hernqvist H, Lauritsen K, et al. Quality of life in patients with heartburn but without esophagitis: effects of treatment with omeprazole. Am J Gastroenterol. 1999; 94:1782-9.
123. Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002; 97:575-83.
124. Crawley JA, Schmitt CM. How satisfied are chronic heartburn suffers with their prescription medications? Results of the patients unment study. JCOM. 2000;7:29-34.
125. Bredenoord AJ, Dent J. Proton pump inhibitor-therapy refractory gastro-oesophageal reflux disease patients, who are they? Gut. 2007; 56:593-4.
126. Fass R. Proton-pump inhibitor therapy in patients with gastro-oesophageal reflux disease: putative mechanisms of failure. Drugs. 2007; 67:1521-30.
127. The Gallup Organisation: Gallup study of consumer´s use of stomach relief products. Princeton /NJ, The Gallup organisation, 2000.
128. Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology. 2001; 120:1599-606.
129. el-Omar E, Banerjee S, Wirz A, Penman I, Ardill JE, McColl KE. Marked rebound acid hypersecretion after treatment with ranitidine. Am J Gastroenterol. 1996; 91:355-9.
130. Frislid K, Aadland E, Berstad A. Augmented postprandial gastric acid secretion due to exposure to ranitidine in healthy subjects. Scand J Gastroenterol. 1986; 21:119-22.
131. Fullarton GM, Macdonald AM, McColl KE. Rebound hypersecretion after H2-antagonist withdrawal--a comparative study with nizatidine, ranitidine and famotidine. Aliment Pharmacol Ther. 1991; 5:391-8.
132. Fullarton GM, McLauchlan G, Macdonald A, Crean GP, McColl KE. Rebound nocturnal hypersecretion after four weeks treatment with an H2 receptor antagonist. Gut. 1989; 30:449-54.

133. Kummer AF, Johnston DA, Marks IN, Young GO, Tigler-Wybrandi NA, Bridger SA. Changes in nocturnal and peak acid outputs after duodenal ulcer healing with sucralfate or ranitidine. Gut. 1992; 33:175-8.
134. Nwokolo CU, Smith JT, Sawyerr AM, Pounder RE. Rebound intragastric hyperacidity after abrupt withdrawal of histamine H2 receptor blockade. Gut. 1991: 32:1455-60.
135. Prewett EJ, Hudson M, Nwokolo CU, Sawyerr AM, Pounder RE. Nocturnal intragastric acidity during and after a period of dosing with either ranitidine or omeprazole. Gastroenterology. 1991; 100:873-7.
136. Bell N, Karol MD, Sachs G, Greski-Rose P, Jennings DE, Hunt RH. Duration of effect of lansoprazole on gastric pH and acid secretion in normal male volunteers. Aliment Pharmacol Ther. 2001; 15:105-13.
137. Lind T, Cederberg C, Ekenved G, Haglund U, Olbe L. Effect of omeprazole--a gastric proton pump inhibitor--on pentagastrin stimulated acid secretion in man. Gut. 1983; 24:270-6.
138. Sharma B, Axelson M, Pounder RP, Lundborg P, Ohman M, Santana A, et al. Acid secretory capacity and plasma gastrin concentration after administration of omeprazole to normal subjects. Aliment Pharmacol Ther. 1987; 1:67-76.
139. Sharma BK, Walt RP, Pounder RE, Gomes MD, Wood EC, Logan LH. Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. Gut. 1984; 25:957-64.
140. Robert A, Olafsson AS, Lancaster C, Zhang WR. Interleukin-1 is cytoprotective, antisecretory, stimulates PGE2 synthesis by the stomach, and retards gastric emptying. Life Sci. 1991; 48:123-34.
141. Wallace JL, Cucala M, Mugridge K, Parente L. Secretagogue-specific effects of interleukin-1 on gastric acid secretion. Am J Physiol. 1991; 261:G559-64.
142. Eissele R, Brunner G, Simon B, Solcia E, Arnold R. Gastric mucosa during treatment with lansoprazole: Helicobacter pylori is a risk factor for argyrophil cell hyperplasia. Gastroenterology. 1997; 112:707-17.
143. Kuipers EJ, Uyterlinde AM, Pena AS, Hazenberg HJ, Bloemena E, Lindeman J, et al. Increase of Helicobacter pylori-associated corpus gastritis during acid suppressive therapy: implications for long-term safety. Am J Gastroenterol. 1995; 90:1401-6.
144. Jones DB, Howden CW, Burget DW, Silletti C, Hunt RH. Alteration of H2 receptor sensitivity in duodenal ulcer patients after maintenance treatment with an H2 receptor antagonist. Gut. 1988; 29:890-3.
145. Sandvik AK, Brenna E, Waldum HL. Review article: the pharmacological inhibition of gastric acid secretion--tolerance and rebound. Aliment Pharmacol Ther. 1997; 11:1013-8.
146. Wilder-Smith CH, Ernst T, Gennoni M, Zeyen B, Halter F, Merki HS. Tolerance to oral H2-receptor antagonists. Dig Dis Sci. 1990; 35:976-83.
147. Raghunath AS, O'Morain C, McLoughlin RC. Review article: the long-term use of proton-pump inhibitors. Aliment Pharmacol Ther. 2005; 22 Suppl 1:55-63.
148. Smith AD, Gillen D, Cochran KM, El-Omar E, McColl KE. Dyspepsia on withdrawal of ranitidine in previously asymptomatic volunteers. Am J Gastroenterol. 1999; 94:1209-13.
149. Strid H, Simren M, Johansson AC, Svedlund J, Samuelsson O, Bjornsson ES. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being. Nephrol Dial Transplant. 2002; 17:1434-9.

150. Dimenas E, Carlsson G, Glise H, Israelsson B, Wiklund I. Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. Scand J Gastroenterol Suppl. 1996; 221:8-13.
151. Dimenas E, Glise H, Hallerback B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? Scand J Gastroenterol. 1993; 28:681-7.
152. Svedlund J, Sjodin I, Dotevall G. GSRS--a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988; 33:129-34.
153. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67:361-70.
154. Drossman DA, Corazzziari E, Talley NJ, Thompson WG, Whitehead WE. Functional Gastrointestinal Disorders. 2nd edn McLean, VA, USA: Degnon Association. 2000 ;pp:669-88.
155. el-Omar EM, Banerjee S, Wirz A, McColl KE. The Glasgow Dyspepsia Severity Score--a tool for the global measurement of dyspepsia. Eur J Gastroenterol Hepatol. 1996; 8:967-71.
156. Wenger NK, Mattson ME, Furberg CD, Elinson J. Assessment of quality of life in clinical trials of cardiovascular therapies. Am J Cardiol. 1984; 54:908-13.
157. Herlitz J, Caidahl K, Wiklund I, Sjoland H, Karlson BW, Karlsson T, et al. Impact of a history of diabetes on the improvement of symptoms and quality of life during 5 years after coronary artery bypass grafting. J Diabetes Complications. 2000; 14:314-21.
158. Hjortswang H, Jarnerot G, Curman B, Sandberg-Gertzen H, Tysk C, Blomberg B, et al. The influence of demographic and disease-related factors on health-related quality of life in patients with ulcerative colitis. Eur J Gastroenterol Hepatol. 2003; 15:1011-20.
159. Mustalahti K, Lohiniemi S, Collin P, Vuolteenaho N, Laippala P, Maki M. Gluten-free diet and quality of life in patients with screen-detected celiac disease. Eff Clin Pract. 2002; 5:105-13.
160. Shaw MJ, Talley NJ, Beebe TJ, Rockwood T, Carlsson R, Adlis S, et al. Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. Am J Gastroenterol. 2001; 96:52-7.
161. Nocon M, Kulig M, Leodolter A, Malfertheiner P, Willich SN. Validation of the Reflux Disease Questionnaire for a German population. Eur J Gastroenterol Hepatol. 2005; 17:229-33.
162. Jones R, Coyne K, Wiklund I. The gastro-oesophageal reflux disease impact scale: a patient management tool for primary care. Aliment Pharmacol Ther. 2007; 25:1451-9.
163. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993; 31:247-63.
164. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992; 30(5 Suppl):MS253-65.
165. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30:473-83.
166. Kaplan-Machlis B, Spiegler GE, Revicki DA. Health-related quality of life in primary care patients with gastroesophageal reflux disease. Ann Pharmacother. 1999; 33:1032-6.

167. Revicki DA, Wood M, Maton PN, Sorensen S. The impact of gastroesophageal reflux disease on health-related quality of life. Am J Med. 1998; 104:252-8.
168. Wiklund IK, Junghard O, Grace E, Talley NJ, Kamm M, Veldhuyzen van Zanten S, et al. Quality of Life in Reflux and Dyspepsia patients. Psychometric documentation of a new disease-specific questionnaire (QOLRAD). Eur J Surg Suppl. 1998; 583:41-9.
169. Hegedus O, Ryden J, Rehnberg AS, Nilsson S, Hellstrom PM. Validated accuracy of a novel urea breath test for rapid Helicobacter pylori detection and in-office analysis. Eur J Gastroenterol Hepatol. 2002; 14:513-20.
170. de Morais SM, Wilkinson GR, Blaisdell J, Nakamura K, Meyer UA, Goldstein JA. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem. 1994; 269:15419-22.
171. Goudie BM, McKenzie PE, Cipriano J, Griffin EM, Murray FE. Repeat prescribing of ulcer healing drugs in general practice--prevalence and underlying diagnosis. Aliment Pharmacol Ther. 1996; 10:147-50.
172. Ryder SD, O'Reilly S, Miller RJ, Ross J, Jacyna MR, Levi AJ. Long term acid suppressing treatment in general practice. Bmj. 1994; 308:827-30.
173. Pham CQ, Regal RE, Bostwick TR, Knauf KS. Acid suppressive therapy use on an inpatient internal medicine service. Ann Pharmacother. 2006; 40:1261-6.
174. Wadibia EC, Lucas BD, Hilleman DE, Mooss AN. Economic impact of inappropriate histamine2-receptor antagonist use. Clin Ther. 1997; 19:1085-91.
175. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med. 1994; 236:619-32.
176. Jacobson BC, Ferris TG, Shea TL, Mahlis EM, Lee TH, Wang TC. Who is using chronic acid suppression therapy and why? Am J Gastroenterol. 2003; 98:51-8.
177. Stein MR, Towner TG, Weber RW, Mansfield LE, Jacobson KW, McDonnell JT, et al. The effect of theophylline on the lower esophageal sphincter pressure. Ann Allergy. 1980; 45:238-41.
178. Ekstrom T, Tibbling L. Influence of theophylline on gastro-oesophageal reflux and asthma. Eur J Clin Pharmacol. 1988; 35:353-6.
179. Hubert D, Gaudric M, Guerre J, Lockhart A, Marsac J. Effect of theophylline on gastroesophageal reflux in patients with asthma. J Allergy Clin Immunol. 1988; 81:1168-74.
180. Sontag SJ, O'Connell S, Khandelwal S, Miller T, Nemchausky B, Schnell TG, et al. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology. 1990; 99:613-20.
181. Richter JE. Gastrooesophageal reflux disease. Best Pract Res Clin Gastroenterol. 2007; 21:609-31.
182. Grime J, Pollock K, Blenkinsopp A. Proton pump inhibitors: perspectives of patients and their GPs. Br J Gen Pract. 2001; 51:703-11.
183. Krag A, Teglbjerg LS, Malchow-Moller A, Hallas J, Bytzer P. Prescribing of acid suppressive therapy: interactions between hospital and primary care. Aliment Pharmacol Ther. 2006; 23:1713-8.
184. Kempainen RR, Savik K, Whelan TP, Dunitz JM, Herrington CS, Billings JL. High prevalence of proximal and distal gastroesophageal reflux disease in advanced COPD. Chest. 2007; 131:1666-71.
185. Wiklund I, Glise H, Jerndal P, Carlsson J, Talley NJ. Does endoscopy have a positive impact on quality of life in dyspepsia? Gastrointest Endosc. 1998; 47:449-54.
186. Carlsson R, Dent J, Watts R, Riley S, Sheikh R, Hatlebakk J, et al. Gastro-oesophageal reflux disease in primary care: an international study of different

treatment strategies with omeprazole. International GORD Study Group. Eur J Gastroenterol Hepatol. 1998 Feb;10(2):119-24.
187. Inadomi JM, McIntyre L, Bernard L, Fendrick AM. Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. Am J Gastroenterol. 2003; 98:1940-4.
188. Heading RC, Bardhan KD, Sander P. Application of the complete remission concept: many patients with GERD are incompletely treated by standard proton pump inhibitors (PPI) regimen. Gut. 2006;55 Suppl 5:A62.
189. Marrero JM, de Caestecker JS, Maxwell JD. Effect of famotidine on oesophageal sensitivity in gastro-oesophageal reflux disease. Gut. 1994; 35:447-50.
190. Trivedi A, Long JD. Heartburn refractory to proton-pump inhibitors. Curr Treat Options Gastroenterol. 2007; 10:47-56.
191. Watson RG, Tham TC, Johnston BT, McDougall NI. Double blind cross-over placebo controlled study of omeprazole in the treatment of patients with reflux symptoms and physiological levels of acid reflux--the "sensitive oesophagus". Gut. 1997; 40:587-90.
192. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol. 2005; 100:283-9.
193. McColl E, Junghard O, Wiklund I, Revicki DA. Assessing symptoms in gastroesophageal reflux disease: how well do clinicians' assessments agree with those of their patients? Am J Gastroenterol. 2005; 100:11-8.
194. Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol. 1996; 91:1532-8.
195. Pezanoski J, Guanaratnam N, Cowen M. Correct and incorrect dosing of proton pump inhibitors and its impact on GERD symptoms. Gastroenterology. 2003;124((Suppl):A228).
196. Chey WD, Inadomi JM, Booher AM, Sharma VK, Fendrick AM, Howden CW. Primary-care physicians' perceptions and practices on the management of GERD: results of a national survey. Am J Gastroenterol. 2005; 100:1237-42.
197. Organisation TG. Gallup study of consumer´s use of stomach relief products. Princeton/NJ, The Gallup Organisation 2000.
198. Kleveland O, Syversen U, Slordahl K, Waldum HL. Hypergastrinemia as a cause of chromogranin a increase in blood in patients suspected to have neuroendocrine tumor. Digestion. 2001; 64:71-4.
199. Sanduleanu S, De Bruine A, Stridsberg M, Jonkers D, Biemond I, Hameeteman W, et al. Serum chromogranin A as a screening test for gastric enterochromaffin-like cell hyperplasia during acid-suppressive therapy. Eur J Clin Invest. 2001; 31:802-11.
200. Waldum HL, Syversen U. Serum chromogranin A in the control of patients on long-term treatment with inhibitors of acid secretion. Eur J Clin Invest. 2001; 31:741-3.
201. Bjornsson E, Abrahamsson H, Simren M, Mattsson N, Jensen C, Agerforz P, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006; 24:945-54.
202. Gillen D, Wirz AA, Neithercut WD, Ardill JE, McColl KE. Helicobacter pylori infection potentiates the inhibition of gastric acid secretion by omeprazole. Gut. 1999; 44:468-75.

203. Van Soest EM, Siersema PD, Dieleman JP, Sturkenboom MC, Kuipers EJ. Persistence and adherence to proton pump inhibitors in daily clinical practice. Aliment Pharmacol Ther. 2006; 24:377-85.