LONG-TERM TREATMENT OF GASTRO-OESOPHAGEAL REFLUX DISEASE IN PRIMARY CARE

ALIKE VAN DER VELDEN

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Research described in this thesis was performed at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands.
Thesis, with a summary in Dutch.

ONDERHOUDSBEHANDELING VAN REFLUXZIEKTE IN DE HUISARTSPRAKTIJK

Proefschrift, met een samenvatting in het Nederlands.

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CONTENTS

Salutation to the Dawn

Look to this day
for it is life
the very life of life.

In its brief course lie all
the verities and realities of existence
the bliss of growth
the glory of action
the splendor of beauty.

For yesterday is but a dream
and tomorrow is only a vision.
But today well lived
makes every yesterday
a dream of happiness
and every tomorrow
a vision of hope.

Look well, therefore, to this day!

~ ancient Sanskrit poem ~

1

General Introduction

GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux disease (GORD) has a high prevalence in Western countries, where approximately 10 to 20% of the adult population suffers at least weekly from the main GORD symptoms, heartburn and acid regurgitation [1, 2]. The disease is associated with a decrease in quality of life [3, 4], reduced productivity [5], and an increased risk of complications like stricture, Barrett's oesophagus or oesophageal adenocarcinoma. GORD is a considerable economic burden to society. GORD develops when reflux of stomach contents through the lower oesophageal sphincter causes troublesome symptoms or complications. Although the underlying cause remains uncertain, the key pathophysiological mechanism of GORD appears to be transient relaxation of the lower oesophageal sphincter. Furthermore, sliding hiatus hernia, excessive reflux provoked by impaired oesophageal or gastric clearance, and oesophageal hypersensitivity have been implicated [6, 7]. There is evidence that obesity [8, 9], smoking, frequent consumption of alcohol [10, 11] and psychological distress are risk factors for developing GORD [12-14].
Symptoms and complications of GORD can be effectively treated with acid suppressive medication (ASM), of which proton pump inhibitors (PPI) are more effective than histamine-2-receptor antagonists (H2RA) in controlling symptoms and healing oesophageal lesions in short- as well as in long-term treatment [15].

DIAGNOSIS OF GORD

GORD is one of the most common gastrointestinal diseases general practitioners encounter in daily practice; the incidence of patients presenting with GORD-like symptoms is estimated from primary care sentinel practices at 13/1000 registered persons per year (Nivel, Tweede Nationale Studie). Diagnosis of GORD is still imprecise as there is no gold standard for an objective diagnosis. The available tools are a combination of symptom assessment, the PPI test, and invasive procedures like upper gastrointestinal endoscopy, a barium oesophagram and ambulatory pH monitoring [7]. Especially for primary care, where most patients do not have acid-induced oesophageal lesions [16, 17] it is being recognized that GORD can be diagnosed using a symptom-based, patient-centered approach without additional diagnostic testing [18, 19]. The Montreal definition, published in 2006 [20], includes a measure of the severity of symptoms by stating that GORD is "a condition that develops when the reflux of gastric content causes troublesome symptoms or complications". This approach comprises symptom assessment of the cardinal symptoms, heartburn and acid regurgitation, by structured interview or

questionnaires, including asking patients how their symptoms affect their daily lives. Furthermore, attention is being paid to chest pain, sleep disturbances and respiratory symptoms. According to this consensus only a few patients need referral for upper gastrointestinal endoscopy or other diagnostic tests, namely those with symptoms longer than 5 years, symptoms unresolved by standard therapy and those with alarm features (vomiting, gastrointestinal bleeding, anemia, abdominal masses, unexplained weight loss and progressive dysphagia).

For validation of the initial diagnosis, the PPI test is being advocated as a simple, cost-effective tool, which is readily available for general practitioners [21]. As GORD usually is an acid-related disease, a rapid symptomatic response to PPI, although not very specific, is commonly considered to at least partially validate the diagnosis of GORD [22].

Upon referral for upper gastrointestinal endoscopy, oesophagitis and more severe complications of GORD can be evaluated with high specificity. Furthermore, the extent of mucosal injury can be assessed and classified into grade A to D, according to the Los Angeles classification [23]. Endoscopy is invasive and especially in younger patients, in whom serious disease is less likely, the risk of complications may exceed benefits.

MANAGEMENT OF GORD

Several guidelines [20, 24, NICE] have been published on the management of the disease. There is a consensus that PPI therapy is the most effective and should be continued at the lowest dosage that controls symptoms. The composite algorithm derived from several available algorithms for management of GORD will be described [25].

After the initial diagnosis has been made, lifestyle advice and over-the-counter antacid therapy is advocated as first-line management for the disease, although any benefit on symptom control is probably small. Prompt endoscopy is recommended in the presence of alarm symptoms. As most patients do not adequately respond to antacid treatment, current evidence supports initiation of PPI therapy, an empirical trial of 4 to 8 weeks once daily. If symptoms resolve, stepping down therapy has to be considered, and upon inadequate symptom relief, compliance and dosage timing need evaluation. If symptoms continue after dosage adjustment, endoscopy should be considered. Patients with severe oesophagitis (C/D) need maintenance full-dosage PPI therapy. The diagnosis GORD needs to be reconsidered in patients without oesophagitis but still symptomatic on PPI therapy; among others patients could have functional dyspepsia, or symptoms could be caused by non-acid reflux or oesophageal hypersensitivity [26].

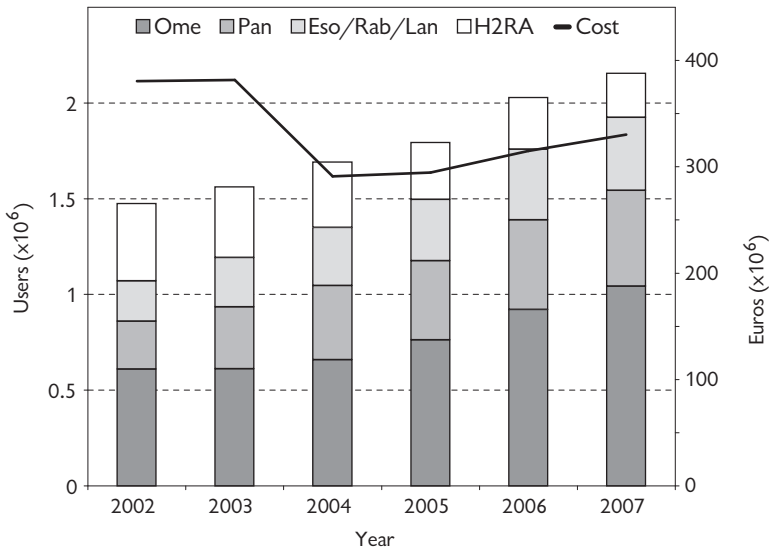


Figure: Trends in acid suppressive medication use by the Dutch population: types and total costs.
Ome: Omeprazole, Pan: Pantopraole, Eso: Esomeprazole, Rab: Rabeprazole, Lan: Lansoprazole, H2RA: Ranitidine, Cimetidine, Famotidine.

Despite straightforwardness of this algorithm, initial empirical treatment with PPIs often evolves in long-term chronic treatment, in which both patients and physicians have their role. Patients quickly adhere to PPIs due to their effective and fast symptom suppression, combined with minor side effects. Besides this high therapy satisfaction a considerable placebo effect is apparent [27], and this placebo effect is further accentuated by relapses and rebound hyperacidity after therapy cessation attempts [28, 29]. Furthermore, a positive PPI test, or response to PPI therapy can erroneously be accepted as proof for GORD; due to a substantial placebo response the specificity of this test is poor [22]. Due to the rebound effect of PPIs even more patients are false-positively labeled. Finally, PPI prescription is often prolonged without interim evaluation and consultation. As a result there is a large group of patients presumably suffering from GORD chronically using acid suppressive medication without an evidence-based indication.

On-demand treatment

Since 2000, on-demand treatment with PPIs has been shown to be an effective and safe alternative in controlling GORD symptoms [30, 31]. Upon first occurrence of symptoms, patients are treated for 4 to 8 weeks with a standard PPI dosage. From then

on, patients are instructed to take medication only in case of recurrent symptoms and to terminate treatment once symptoms are controlled satisfactorily; the patient decides when to start and stop medication use. Despite effectiveness, safety, lower overall costs, and guidelines and health care insurers advocating on-demand treatment, on-demand prescription is only slowly gaining ground [32-34].

Use of acid suppressive medication in the Netherlands

Based on 2007 data from the GIP database (College voor Zorgverzekeringen), 12% of the total Dutch population uses acid suppressive medication (ASM). About 25% of them can be classified as long-term chronic user (Stichting Farmaceutische Kengetallen). PPIs are used by 88% and H2RAs by 12% (Figure). The yearly costs for ASM amount to €330 million, which is 6.5% of the annual national pharmacotherapy budget. The decrease in total costs around 2004 was caused by the Omeprazole patent expiry; costs for a daily dosage decreased from €1.39 to €0.62, and are currently €0.04.

STUDY POPULATION AND PROTOCOL OF THE ELISE STUDY

Results described in this thesis are based on the 288 patients included in the ELISE study; they were recruited from primary care practices in Deventer, Olst, Bathmen, Diepenveen, Holten, Markelo, Twello, Schalkhaar, Hengelo, Utrecht, Bunnik and de Bilt. Patients had a history of GORD or GORD-like symptoms and used long-term, chronic ASM to control their symptoms. The general practitioner included patients in the study, only if they did not have an evidence-based indication for long-term chronic use, like a history of oesophagitis C/D, Barrett's oesophagus, acute peptic ulcers or chronic use of non-steroidal anti-inflammatory drugs (Dyspepsia NICE, 2004). In this respect, patients were eligible to reduce or even terminate their ASM treatment with a minimal risk for severe complications resulting from ASM withdrawal.
To be able to characterize the patients, medical files were screened for disease- and medication history, patients were questioned for demographic and lifestyle variables, and filled out questionnaires regarding residual reflux symptoms, generic quality of life and psychological state.
At study entry, all patients were transferred for 4 weeks to the same treatment, daily Pantoprazole 20 mg. In order to determine the minimal effective dosage with minimal interference by placebo effects, we used a 'fixed regime rescue' protocol. Patients received 2 containers with capsules, one for daily use and one with rescue capsules. Patients were instructed to routinely use one capsule per day from the daily-container, and in case of inadequate symptom control one capsule daily from the rescue-

container; patients decided when to start and stop rescue medication use by acting on symptoms. Randomization group 1 had placebo in their daily container and Pantoprazole in the container "if necessary"; these patients blindly adjusted their dosage. Group 2 received daily Pantoprazole and had placebo in the "if necessary" container; this group served as a control, and was needed to make the patients unaware of their regime.

OBJECTIVES OF THIS THESIS

The first objective of this thesis is to characterize the group of GORD patients on long-term chronic ASM with respect to lifestyle, *Helicobacter pylori* status and psychological state in relation to residual reflux symptoms and to the amount of medication they use. The second objective is to investigate whether this group of patients is able to reduce or terminate their acid suppressive therapy, with the aim to identify patient characteristics predicting eligibility for successful transfer to on-demand therapy after long-term chronic treatment.
The final objective is to evaluate the practical use of a prediction rule which upon initial presentation of GORD-like symptomatology might help in decisions concerning re-evaluation, treatment options and referral.

OUTLINE OF THIS THESIS

Chapter 2 provides the characterization of patients included in the trial. In *chapter 2.1* prevalences of overweight, smoking and use of alcohol are compared to the prevalences found in the general Dutch population, and these lifestyle characteristics are related to the degree of symptom control and to the amount of medication the patients use. *Chapter 2.2* provides a comparison between *Helicobacter pylori* positive and negative patients with respect to the amount of medication they need to control their symptoms. In *chapter 2.3* the psychological state and generic quality of life of these patients is reported. *Chapter 3* compares the subgroup of patients who report residual reflux symptoms despite their chronic medication with the subgroup reporting complete symptomatic relief in order to identify patient characteristics associated with incomplete symptom control.
The primary results of the intervention of the ELISE study are presented in *chapter 4*. In a blinded way we investigated how much ASM this group of patients actually needs to control their symptoms, and whether a reduction in medication use affects symptom control and quality of life. *Chapter 5* presents the analysis on predicting eligibility for successful dosage reduction after long-term chronic treatment.

In order to make a better initial choice for treatment of patients presenting with symptoms indicative of GORD (re-evaluation, empirical PPI treatment, or prompt upper gastrointestinal endoscopy), the practical consequences of the use of a prediction rule are evaluated in *chapter 6*.

Finally, in *chapter 7* we discuss the overall findings reported in this thesis, the advantages and disadvantages of the chosen protocol, and present two concepts on how to deal with patients with uncomplicated GORD on chronic medication in primary care.

REFERENCES

1. Delaney BC. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004;20(Suppl 8):2-4.
2. Moayyedi P, Axon AT. Review article: gastro-oesophageal reflux disease-the extent of the problem. *Aliment Pharmacol Ther* 2005;22(Suppl 1):11-19.
3. Pace F, Negrini C, Wiklund I, Rossi C, Savarino V. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005;22:349-356.
4. Prasad M, Rentz AM, Revicki DA. The impact of treatment for gastro-oesophageal reflux disease on health-related quality of life: a literature review. *Pharmacoeconomics* 2003;21:769-790.
5. Leodolter A, Nocon M, Kulig M, Willich SN, Malfertheiner P, Labenz J. Gastro esophageal reflux disease is associated with absence from work: results from a prospective cohort study. *World J Gastroenterol* 2005;11:7148-7151.
6. Boeckxstaens GE. Review article: the pathophysiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007;26:149-160.
7. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet* 2006;367:2086-2100.
8. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143:199-211.
9. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006;354:2340-2348.
10. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. *Gut* 2004;53:1730-1735.
11. Nocon M, Keil T, Willich SN. Prevalence and sociodemographics of reflux symptoms in Germany-results from a national survey. *Aliment Pharmacol Ther* 2006;23:1601-1605.
12. Ålander T, Svardsudd K, Johansson SE, Agreus L. Psychological illness is commonly associated with functional gastrointestinal disorders and is important to consider during patient consultation: a population-based study. *BMC Med* 2005;3:8.

13. Locke GR, Weaver AL, Melton LJ, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004;99:350-357.
14. Wright CE, Ebrecht M, Mitchell R, Anggiansah A, Weinman J. The effect of psychological stress on symptom severity and perception in patients with gastro-oesophageal reflux. *J Psychosom Res* 2005;59:415-424.
15. 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;15:765-772.
16. Lind T, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, Junghard O, Lauritsen K, Lundell L, Pedersen SA, Stubberöd A. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997;32:974-979.
17. Quartero AO, Numans ME, de Wit NJ. More abnormalities at upper endoscopy than expected by the General Practitioner. *Huisarts Wet* 2001;44:590-594.
18. Fass R. Symptom assessment tools for gastroesophageal reflux disease (GERD) treatment. *J Clin Gastroenterol* 2007;41:437-444.
19. Flook N, Jones R, Vakil N. Approach to gastroesophageal reflux disease in primary care: Putting the Montreal definition into practice. *Can Fam Physician* 2008;54:701-705.
20. 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;101:1900-1920.
21. Fass R. Empirical trials in treatment of gastroesophageal reflux disease. *Dig Dis* 2000;18:20-26.
22. Numans ME, Lau J, de Wit NJ, Bonis PA. Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. *Ann Intern Med* 2004;140:518-527.
23. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172-180.
24. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Am J Gastroenterol* 2005;100:190-200.
25. Ali T, Miner PB. New developments in gastroesophageal reflux disease diagnosis and therapy. *Curr Opin Gastroenterol* 2008;24:502-508.
26. Bredenoord AJ, Smout AJ. Refractory gastrooesophageal reflux disease. *Eur J Gastroenterol Hepatol* 2008;20:217-223.

27. Pace F, Maconi G, Molteni P, Minguzzi M, Bianchi PG. Meta-analysis of the effect of placebo on the outcome of medically treated reflux esophagitis. *Scand J Gastroenterol* 1995;30:101-105.
28. Carlsson R, Galmiche JP, Dent J, Lundell L, Frison L. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. *Aliment Pharmacol Ther* 1997;11:473-482.
29. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. *Aliment Pharmacol Ther* 2005;21:149-154.
30. Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On-demand therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 2007;102:642-653.
31. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Aliment Pharmacol Ther* 2007;26:195-204.
32. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. *Postgrad Med J* 2007;83:66-68.
33. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008;336:2-3.
34. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, Malfertheiner P, Willich SN. Long-term treatment of patients with gastro-oesophageal reflux disease in routine care-results from the ProGERD study. *Aliment Pharmacol Ther* 2007;25:715-722.

2.1

GORD Patients on Chronic Acid Suppressive Medication: Overweight Impairs Symptom Control

ABSTRACT

Overweight is a risk factor for symptomatic gastro-oesophageal reflux disease. In a cross-sectional study in primary care we analyzed the influence of overweight on symptom control in GORD patients treated with chronic acid suppressive medication. We found that overweight increased the prevalence and severity of residual reflux symptoms; no effect was found of smoking and alcohol. GORD patients with overweight should be advised -in addition to medication- to lose weight for sustained and adequate symptom control.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD), with symptoms of heartburn and acid regurgitation is experienced by 10 to 30% of the population at least weekly [1, 2]. Large general population-based studies have shown that overweight and obesity are risk factors for symptomatic GORD [3-5]. A dose-dependent association was found between BMI and symptom severity and frequency of untreated GORD [6]. Smoking and frequent consumption of alcohol were also found to be associated with increased symptoms [7, 8], although some report otherwise [9].

GORD symptoms are effectively treated by acid suppressive medication (ASM), proton pump inhibitors (PPIs) are most commonly used [10]. However, ineffectiveness of PPI pharmacotherapy has become a common clinical issue; up to 30% of GORD patients remains symptomatic on standard PPI treatment [11].

Identification of lifestyle characteristics influencing the adequacy of symptom control under ASM treatment is of high relevance in GORD treatment. In a cross-sectional study in primary care we explored whether overweight, smoking and alcohol consumption influence the prevalence and severity of residual reflux symptoms in patients on chronic ASM.

METHODS

Participants

288 primary care patients with uncomplicated GORD (excluding documented Barrett's oesophagus, oesophagitis C/D, acute peptic ulcer disease or serious co-morbidity) treated with minimally 180 defined daily dosages (DDD) of ASM per year.

Measurements

Data on ASM in use, BMI (kg/m^2), current smoking (yes, no) and alcohol consumption (never/rarely, <3, ≥3 consumptions/day) were obtained and patients completed the following questionnaires:

Quality of life in reflux and dyspepsia (QolRad)

QolRad outcome reflects impact of (residual) reflux symptoms and treatment response [12]. It includes 25 disease-related quality of life items combined into 5 dimensions: emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning. A 7-point scale is used to assess item severity or frequency (1: a great deal/all of the time, 2: a lot/most, 3: a moderate amount/quite a lot, 4: some, 5: a little, 6: hardly any, 7: none).

Symptom check list 90 (SCL-90)

This validated questionnaire reflects psychological symptom state [13]. It covers 8 dimensions of mental health (anxiety, phobic anxiety, depression, somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility, sleeping problems). As psychological distress has been shown to be associated with both gastrointestinal symptomatology [14] and overweight [15], SCL-90 results were used to identify potential confounding by psychopathology.

Data analysis

Prevalences of overweight, smoking and alcohol consumption in the patient population were compared to the Dutch population (2005, Dutch Statistical Office, http://statline.cbs.nl); pooled Mantel-Haenszel prevalence ratios were calculated after stratification for gender and age. Mean values were compared using the Students t-test and one-way ANOVA, dichotomous variables with the χ^2-test (SPSS version 14.0); two-sided p-values less than 0.05 were considered significant.

RESULTS

Overweight and obesity were highly prevalent among GORD patients on chronic ASM; 72% had overweight (BMI ≥25) and 23% obesity (BMI ≥30). Comparison with the Dutch population showed prevalence ratios of respectively 1.3 (95% CI: 1.2-1.4) and 1.7 (CI: 1.4-2.1). Contrarily, prevalences of smoking, any and high alcohol were lower than in the population, with ratios of respectively 0.7 (CI: 0.5-0.8), 0.6 (CI: 0.6-0.7) and 0.5 (CI: 0.3-0.8).

Table: Effect of overweight, smoking and alcohol on symptom control and dosage.

		n	QolRad (mean[1], SD, min-max)		QolRad (% pnt<5)[2]	DDD
Weight	BMI <25	81	6.5* ± 0.7	(3.8-7)	14 *	328
	BMI ≥25	207	6.2* ± 1	(2.2-7)	26 *	358
Smoking	no	228	6.3 ± 0.9	(2.2-7)	22	346
	yes	60	6.3 ± 0.9	(3.0-7)	23	361
Alcohol	no/rarely	132	6.2 ± 1	(2.2-7)	29	361
	<3/day	139	6.4 ± 0.7	(4.2-7)	18	345
	≥3/day	17	6.3 ± 0.9	(3.1-7)	12	293

DDD: defined daily dosage, [1] mean of 5 dimensions, [2] % of patients scoring lower than 5 on at least one dimension, * $p<0.05$.

Of these lifestyle factors, only overweight was associated with inadequate symptom control despite chronic medication (Table). Overweight patients scored significantly lower on all five QolRad dimensions ($p=0.01$ for the mean value). Furthermore, a higher percentage of overweight patients scored lower than 5 on one or more QolRad dimensions ($p=0.04$). These differences could not be explained by smoking or alcohol, as these factors did not influence symptom control, and neither by differences in ASM dosage used. Overweight patients even tended to use higher dosages than patients with normal weight (Table). Finally, inadequate symptom control was not caused by confounding by psychological distress; SCL-90 values of patients with normal- and overweight were comparable ($p>0.3$ for all dimensions, not shown).

DISCUSSION

The impact of BMI on the prevalence, severity and frequency of GORD-related symptoms has been established in the population [3-6]. Additionally, we have shown that under chronic acid suppression the prevalence and severity of residual symptoms are increased by overweight as well.

Residual symptoms in GORD patients are associated with impaired generic quality of life [16], and high costs due to frequent consultations, diagnostic tests and dosage escalations. From a patients', clinicians' and public health perspective, relieving residual symptoms by lifestyle modifications is an important issue, also given the simultaneous rise in the prevalences of overweight and GORD. Our study indicates that weight reduction might be beneficial in controlling residual symptoms, and

thereby prevents unnecessary dosage elevation. A potential problem of our study is that symptom severity was also shown to be associated with dietary habits, physical activity, amount of smoking and kinds of alcohol [8], which were not considered in our study. However, Jacobson *et al.* described that the association between BMI and symptoms in the population did not alter after controlling for these variables [6], and we did include smoking, amount of alcohol and psychological distress.

Intra-abdominal pressure, the number and duration of reflux episodes [17], transient lower oesophageal sphincter relaxation [18] and hiatus hernia have been shown to correlate with BMI. It has been proposed that via these phenomena overweight predisposes to GORD, and they could as well mediate in inadequate relief in medication-treated patients.

In 1999 it was already described that weight loss had a beneficial effect on GORD symptoms in untreated individuals [19]. Overweight patients on maintenance therapy consulting because of inadequately controlled GORD symptoms should be advised that in addition to their medication weight reduction might help to better control their symptoms. This is also applicable for patients with marginal overweight, as independent of BMI recent weight gain has also shown to be associated with symptoms [20]. A recently developed concept for primary care promotes preventing further weight gain, rather than losing weight [21]. The effects of weight reduction or stability programs on residual GORD symptoms and on the dosage giving relief should be further evaluated.

REFERENCES

1. Delaney BC. Review article: prevalence and epidemiology of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004;20(Suppl 8):2-4.
2. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;54:710-717.
3. Corley DA, Kubo A. Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2006;101:2619-2628.
4. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;143:199-211.
5. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA* 2003;290:66-72.
6. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006;354:2340-2348.
7. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux. *Gut* 2004;53:1730-1735.

8. Nocon M, Keil T, Willich SN. Prevalence and sociodemographics of reflux symptoms in Germany-results from a national survey. *Aliment Pharmacol Ther* 2006;23:1601-1605.
9. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006;166:965-971.
10. 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.
11. 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.
12. Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol* 2001;96:1998-2004.
13. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry* 1976;128:280-289.
14. Ålander T, Svardsudd K, Johansson SE, Agreus L. Psychological illness is commonly associated with functional gastrointestinal disorders and is important to consider during patient consultation: a population-based study. *BMC Med* 2005;3:8.
15. Petry NM, Barry D, Pietrzak RH, Wagner JA. Overweight and obesity are associated with psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychosom Med* 2008;70:288-297.
16. 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* 2003;18:767-776.
17. El-Serag HB, Ergun GA, Pandolfino J, Fitzgerald S, Tran T, Kramer JR. Obesity increases oesophageal acid exposure. *Gut* 2007;56:749-755.
18. Wu JC, Mui LM, Cheung CM, Chan Y, Sung JJ. Obesity is associated with increased transient lower esophageal sphincter relaxation. *Gastroenterology* 2007;132:883-889.
19. Fraser-Moodie CA, Norton B, Gornall C, Magnago S, Weale AR, Holmes GK. Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. *Scand J Gastroenterol* 1999;34:337-340.
20. Rey E, Moreno-Elola-Olaso C, Artalejo FR, Locke GR, Diaz-Rubio M. Association between weight gain and symptoms of gastroesophageal reflux in the general population. *Am J Gastroenterol* 2006;101:229-233.
21. Pryke R, Docherty A. Obesity in primary care: evidence for advising weight constancy rather than weight loss in unsuccessful dieters. *Br J Gen Pract* 2008;58:112-117.

2.2

GORD Patients on Chronic Acid Suppressive Medication: *Helicobacter Pylori* Infection Reduces Medication Necessity

ABSTRACT

Infection with *Helicobacter pylori* was shown to interfere with the efficacy of acid suppressive medication (ASM). However, this effect has not been studied in long-term treated patients. We compared the dosages used for symptom relief between *H. pylori* positive and negative gastro-oesophageal reflux disease patients. *H. pylori* positive patients used a significantly lower dosage than uninfected patients (303 versus 360 defined daily dosages per year). Our study confirms that *H. pylori* status must be taken into account in studies on dosage defining and treatment efficacy in GORD. Furthermore, dosage adjustment could be necessary after eradication of *H. pylori* in GORD patients.

INTRODUCTION

Helicobacter pylori infection is important in the etiology of peptic ulcers, but does not seem to have a role in pathogenesis of gastro-oesophageal reflux disease (GORD). Epidemiological data indicate that infection might even be "protective". This was suggested by a lower prevalence of *H. pylori* in GORD patients [1], more severe reflux symptoms in *H. pylori* negative patients [2], and exacerbation of GORD after *H. pylori* eradication [3].

The most effective therapy for GORD patients is gastric acid suppression. There is compelling evidence that the efficacy of acid suppressive medication (ASM) is increased in the presence of a *H. pylori* infection [4]. Intragastric pH after 1 week of Omeprazole was 5.5 in *H. pylori* positive-, and 4.0 in negative healthy volunteers [5], and better acid suppression by Omeprazole was seen before *H. pylori* eradication [6]. Contradictory results have been reported with respect to the clinical implication of *H. pylori* status. Healing of oesophagitis and symptom control by Pantoprazole were higher in *H. pylori* infected patients [7], but Rabeprazole was equally effective in GORD patients with or without infection [8].

It can be expected that *H. pylori* infected patients require less medication for symptom control, but to date further evidence to confirm this hypothesis is lacking. We determined the impact of *H. pylori* infection on the effective dosage used by GORD patients on long-term ASM. In primary care practice, standard ASM treatment is initiated at disease onset. From then on, the dosage will be increased for patients with inadequately controlled symptoms, or decreased when satisfied patients take ASM non-continuously in a self-determined pattern.

METHODS

Participants

This study was carried out with entrance data from primary care patients on long-term ASM, willing to participate in a trial on dosage adjustment. Patients were treated for uncomplicated GORD (excluding documented Barrett's oesophagus, oesophagitis C/D, acute peptic ulcer disease, or severe co-morbidity) with minimally 180 defined daily dosages (DDD) of ASM per year, for at least one year.

Measurements

ASM in use (brand, DDD: obtained from local pharmacies), BMI (kg/m^2), current smoking (yes, no), alcohol consumption (never/rarely, yes) and the following questionnaires:

Quality of life in reflux and dyspepsia (QolRad)

QolRad outcome reflects impact of (residual) reflux symptoms and treatment response [9]. It includes 25 disease-related quality of life items combined into 5 dimensions: emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning. A 7-point scale is used to assess item severity or frequency.

Symptom check list 90 (SCL-90)

This validated questionnaire reflects psychological symptom state and covers 8 dimensions of psychological distress and psychopathology [10].

Helicobacter pylori infection

Infection was diagnosed by determining serum IgG antibodies to *H. pylori* using an enzyme-linked immunosorbent assay (Pyloriset EIA-G III, ORION). No international standard is available for cut-off levels; the manufacturer suggests ≥20 IU/ml as *H. pylori* positive. However, when evaluated against reference standards in a primary care setting, values of 30 or 40 IU/ml have been recommended [11]. In our analysis we regarded ≥30 IU/ml as positive.

Data analysis

Mean values were compared using the Students t-test, dichotomous variables with the χ^2-test (SPSS version 14.0); two-sided p-values less than 0.05 were considered significant. Multiple linear regression analysis was used to correct *H. pylori*-dependent DDD for gender, age, BMI, alcohol, smoking, psychological state and residual reflux symptoms. A variable was included in the model if its addition resulted in a β change of at least 10%.

RESULTS

Of 288 included GORD patients on long-term ASM, 16 were excluded from analysis because of unavailability of blood samples (n=12), positive titers after eradication (n=2), and ASM use of less than one year (n=2). Of the remaining 272 patients 25.7% had a *H. pylori* titer of 30 IU/ml or higher.

H. pylori positive patients did not differ from negative patients with respect to gender, BMI, smoking, alcohol use and psychological state; *H. pylori* positive patients were older (Table). Both groups adequately controlled their reflux symptoms, as was reflected by high QolRad scores (6 represents 'hardly any complaints'). However, symptom control by *H. pylori* positive patients was achieved at a lower dosage, 303 DDD per year, versus 360 DDD by the negative group. Furthermore, in the *H. pylori* positive group fewer patients needed at least one daily dosage, and more managed with a histamine-2-receptor antagonist instead of a proton pump inhibitor (Table).

The causal relationship between *H. pylori* infection and DDD necessity was confirmed using multiple linear regression analysis with DDD as dependent variable, resulting in the regression line: DDD=358–55**H. pylori* (95%CI(B): -15 to -95, p=0.017). Adjustment for potential confounding by age, BMI, smoking, alcohol use, psychological state and symptom control did not change the effect of *H. pylori* status on DDD necessity.

DISCUSSION

In primary care patients with GORD we demonstrated that the stable dosage of ASM required for acceptable symptom control depends on *H. pylori* status. *H. pylori* positive patients were found to use a mean of 303 DDD, versus 360 by uninfected patients with the same level of symptom control. *H. pylori* positivity was defined as 30 IU/ml or more on ELISA. This cut-off level resulted in an infection rate of 25.7% which is consistent with the prevalence of *H. pylori* in Dutch primary care [11]. Similar significant effects were however observed if cut-off levels of 35 and 40 IU/ml were used (data not shown). The effective dosage recorded from the patients was not reached during a study, but in the natural way primary care patients and physicians interact. Patients with uncomplicated GORD are prescribed a standard dosage daily at disease onset. This dosage can be increased when symptoms are not controlled satisfactorily, or decreased when adequately controlled patients respond to a lower dosage or take their medication non-continuously [12]. Patients can take these decisions after conferring with their physician, or without consultation.

Table: Patient characteristics according to *H. pylori* status.

	H. pylori negative (n=202)	*H. pylori* positive (n=70)	p-value[3]
Gender (% male)	55	59	0.7
Age (mean ± SD)	55 ± 10.8	61 ± 8.4	<0.001
BMI	27.9 ± 4.9	26.8 ± 3.6	0.07
Smoking (% yes)	21	21	1
Alcohol (% yes)	56	49	0.3
SCL-90[1]	122 ± 32	122 ± 29	1
QolRad[2]	6.3 ± 0.9	6.2 ± 0.9	0.2
DDD	360 ± 160	303 ± 156	0.017
DDD (% pnt ≥360)	58	37	0.004
H2RA (% pnt)	8	19	0.016

[1] Total SCL-90 score, [2] mean of the 5 QolRad dimensions, [3] χ^2-test to qualitative variables and t-test to continuous variables.

Indirect evidence from other studies supports our observation. The severity of GORD symptoms, healing rates, and symptom control have been shown to depend on *H. pylori* status [2, 7, 13]. However, in two studies *H. pylori* infection did not translate to lower dosages. Schenk *et al*. [2] reported no difference in the Omeprazole dosage to maintain symptomatic and endoscopic remission of GORD. Kuipers *et al.* [14] showed that *H. pylori* eradication in GORD patients did not worsen reflux disease, nor increased the Omeprazole dosage. However, sensitivity of these studies can be questioned: high mean dosages were used (40 and 30 mg), the initial dosage of 20 mg was increased in steps of 20 mg, and only in the second study could be lowered to 10 mg. In our natural adjustment setup, patients could also use less than a daily dosage.

Non-continuous therapy is appropriate for patients with uncomplicated GORD. Our study was done in primary care, where more than 90% of oesophagitis is grade A/B [15]. Contrarily, the two clinic-based studies [2, 14] included patients with all grades of oesophagitis and with Barrett's oesophagus. Patients with uncomplicated GORD can often step down to less than daily therapy. During lowering to less than a daily dosage a second positive effect of *H. pylori* has been described. Discontinuation of ASM therapy may result in rebound hypersecretion of gastric acid. Infection with *H. pylori* prevents rebound hypersecretion [16, 17], thereby facilitating dosage reduction.

In conclusion, we demonstrated that infection with *H. pylori* reduces the dosage of ASM required for symptom control. This is not of a magnitude that eradication should be omitted in GORD patients with known infection, especially given the association

between *H. pylori* and gastric cancer [18]. However, after eradication of *H. pylori*, patients with GORD might require a dosage increase to maintain the same level of symptom control. Furthermore, in studies on dosage defining or medication efficacy, *H. pylori* status must be taken into account.

REFERENCES

1. Raghunath A, Hungin AP, Wooff D, *et al*. Prevalence of *Helicobacter pylori* in patients with gastro-oesophageal reflux disease: systematic review. *BMJ* 2003;326:737.
2. Schenk BE, Kuipers EJ, Klinkenberg-Knol EC, *et al*. *Helicobacter pylori* and the efficacy of omeprazole therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 1999;94:884-887.
3. Wu JC, Chan FK, Wong SK, *et al*. Effect of *Helicobacter pylori* eradication on oesophageal acid exposure in patients with reflux oesophagitis. *Aliment Pharmacol Ther* 2002;16:545-552.
4. Martinek J, Kuzela L, Spicak J, *et al*. Review article: the clinical influence of *Helicobacter pylori* in effective acid suppression-implications for the treatment of gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2000;14:979-990.
5. Verdu EF, Armstrong D, Fraser R, *et al*. Effect of *Helicobacter pylori* status on intragastric pH during treatment with omeprazole. *Gut* 1995;36:539-543.
6. Verdu EF, Armstrong D, Idstrom JP, *et al*. Effect of curing *Helicobacter pylori* infection on intragastric pH during treatment with omeprazole. *Gut* 1995;37:743-748.
7. Holtmann G, Cain C, Malfertheiner P. Gastric *Helicobacter pylori* infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999;117:11-16.
8. De Wit NJ, Boer WA, Geldof H, *et al*. Treatment of gastro-oesophageal reflux disease with rabeprazole in primary and secondary care: does *Helicobacter pylori* infection affect proton pump inhibitor effectiveness? *Aliment Pharmacol Ther* 2004;20:451-458.
9. Talley NJ, Fullerton S, Junghard O, *et al*. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol* 2001;96:1998-2004.
10. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry* 1976;128:280-289.
11. Weijnen CF, Hendriks HA, Hoes AW, *et al*. New immunoassay for the detection of *Helicobacter pylori* infection compared with urease test, ^{13}C breath test and histology: validation in the primary care setting. *J Microbiol Methods* 2001;46:235-240.
12. 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.

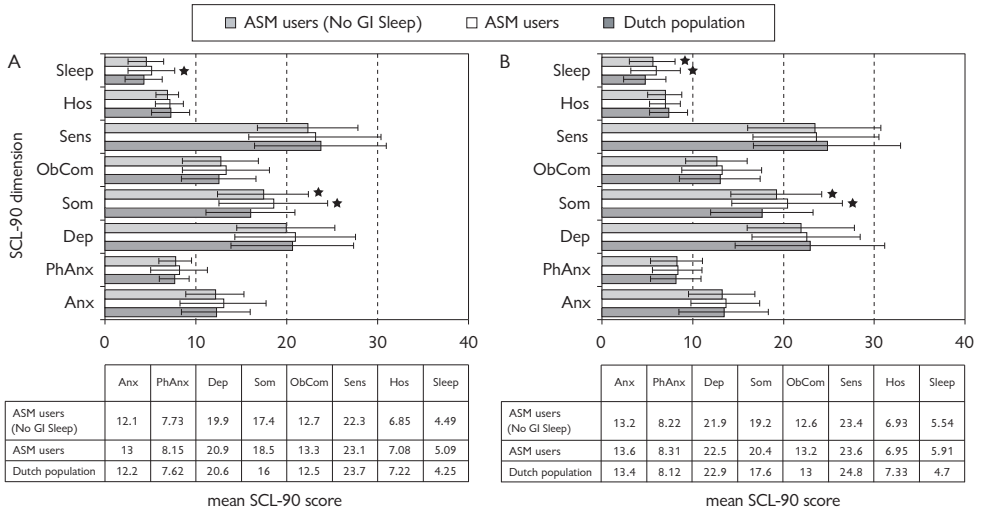
13. Hatlebakk JG, Hyggen A, Madsen PH, *et al*. Heartburn treatment in primary care: randomised, double blind study for 8 weeks. *BMJ* 1999;319:550-553.
14. Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, *et al*. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004;53:12-20.
15. Quartero AO, Numans ME, de Wit NJ. More abnormalities at upper endoscopy than expected by the General Practitioner. *Huisarts Wet* 2001;44:590-594.
16. Gillen D, Wirz AA, Ardill JE, *et al*. Rebound hypersecretion after omeprazole and its relation to on-treatment acid suppression and *Helicobacter pylori* status. *Gastroenterology* 1999;116:239-247.
17. Gillen D, Wirz AA, McColl KE. *Helicobacter pylori* eradication releases prolonged increased acid secretion following omeprazole treatment. *Gastroenterology* 2004;126:980-988.
18. Uemura N, Okamoto S, Yamamoto S, *et al*. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001;345:784-789.

2.3

GORD Patients on Chronic Acid Suppressive Medication: a Population-Average Psychological State

The etiology of gastro-oesophageal reflux disease (GORD) is known to be heterogeneous. Several studies have indicated relationships between GORD and psychological distress like anxiety, depression, somatization, phobia and obsessionality [1, 2]. Initially these relations were explained by 'health-care seeking behavior', but after confirmation in community-based studies [3-5] a causal interaction between psychological distress and reflux disease was considered likely. However, cross-sectional studies with symptomatic patients cannot elucidate cause and effect, leaving the question "does psychological distress cause oesophageal symptomatology or vice versa" unanswered. We aim to add evidence to these interactions by studying the psychological state and quality of life of GORD patients treated with acid suppressive medication (ASM) to relieve their symptoms.

We studied 288 primary care patients treated for at least 6 months for GORD symptomatology. Potential residual symptoms were evaluated with the QolRad questionnaire (1: a great deal, 6: hardly any, 7: none) [6]. Psychological state (SCL-90) and quality of life (SF-36) were compared to Dutch population averages (Students t-test), after gender-stratification for SCL-90- [7, 8] and age-stratification for SF-36 values [9].



	Anx	PhAnx	Dep	Som	ObCom	Sens	Hos	Sleep
ASM users (No GI Sleep)	12.1	7.73	19.9	17.4	12.7	22.3	6.85	4.49
ASM users	13	8.15	20.9	18.5	13.3	23.1	7.08	5.09
Dutch population	12.2	7.62	20.6	16	12.5	23.7	7.22	4.25

	Anx	PhAnx	Dep	Som	ObCom	Sens	Hos	Sleep
ASM users (No GI Sleep)	13.2	8.22	21.9	19.2	12.6	23.4	6.93	5.54
ASM users	13.6	8.31	22.5	20.4	13.2	23.6	6.95	5.91
Dutch population	13.4	8.12	22.9	17.6	13	24.8	7.33	4.7

Figure: Psychological state of ASM-treated GORD patients.
Patients were compared to the Dutch reference group; males (a) and females (b) were analyzed separately. Second, patients without residual gastrointestinal-related sleeping problems were analyzed (75%). Anx: anxiety, PhAnx: phobic anxiety, Dep: depression, Som: somatization, ObCom: obsessive-compulsive behavior, Sens: interpersonal sensitivity, Hos: hostility, Sleep: sleep disturbance. Mean values and standard deviations are shown, * $p<0.01$.

The patients' mean age was 57 (27-74) years and 56% was male. Indications for ASM use, type of medication used and symptom control during treatment are shown in the Table. All dimensions of the patients' generic quality of life (physical and social functioning, role limitations due to physical and emotional problems, body pain, health perception, vitality and mental health) were comparable to Dutch population values (p-values >0.05, not shown), as were the scores on SCL-90 dimensions (phobic) anxiety, depression, obsessive-compulsive behavior, interpersonal sensitivity and hostility. Scores for somatization and sleep disturbance were slightly higher in our study sample (p-value <0.01); the latter predominantly originated from residual gastrointestinal discomfort at night (Figure). The psychological state of patients with a history of oesophagitis did not differ from those without this diagnosis (p-values >0.05, not shown).

Patients experienced satisfying to complete symptom relief given the high mean QolRad scores, and the absence of consultations for gastrointestinal discomfort in the 6 months preceding the measurements. These ASM-treated GORD patients have a psychological state similar to the general population which contrasts the disturbed psychological state reported in literature for symptomatic patients. This indicates that for the majority of GORD patients psychological distress is not inherent to the disease,

Table: Disease, medication characteristics and symptom control of ASM-treated GORD patients.

Indication	
Oesophagitis A/B (%)	35/19
GORD, reflux, pyrosis (%)	39
Hiatus hernia (%)	7
Years since 1st episode (mean, SD)	7.5 ± 5.8
Medication	
PPI/H2RA (%)	90/10
DDD (mean, SD)	350 ± 162
Impact of residual symptoms (mean, SD)	
Emotional distress	6.5 ± 0.9
Sleep disturbance	6.3 ± 1
Food/drink problems	6 ± 1
Physical/social functioning	6.5 ± 0.8
Vitality	6.1 ± 1.1

PPI: proton pump inhibitor, H2RA: histamine-2-receptor antagonist, DDD: defined daily dosage/year.

but probably temporarily generated during symptomatic phases. Three comments should be made. First, comparable to the population means that there is also a subgroup of psychologically distressed patients in our population; a causal interaction could be present in this subgroup. Second, no psychological data were available of these patients during the initial symptomatic phase. Third, due to the primary care setting, patients did not undergo a thorough diagnostic procedure like oesophageal pH-metry or impedance pH-testing [10]. Oesophagitis (classic GORD) was diagnosed in the majority of patients, but functional heartburn could be present in the group diagnosed as GORD/reflux/pyrosis [11]. A mixed population would however not change our conclusion as literature data suggest involvement of psychological distress in both reflux-related and functional disease [1-5, 11, 12].

In conclusion, GORD patients adequately treated with ASM do not only experience symptom relief, but their psychological condition also benefits.

REFERENCES

1. Baker LH, Lieberman D, Oehlke M. Psychological distress in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 1995;90:1797-1803.
2. Kamolz T, Velanovich V. Psychological and emotional aspects of gastroesophageal reflux disease. *Dis Esophagus* 2002;15:199-203.
3. Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? *Scand J Gastroenterol* 2002;37:294-298.
4. Jansson C, Nordenstedt H, Wallander MA, Johansson S, Johnsen R, Hveem K, *et al*. Severe gastro-oesophageal reflux symptoms in relation to anxiety, depression and coping in a population-based study. *Aliment Pharmacol Ther* 2007;26:683-691.
5. Ålander T, Svardsudd K, Johansson SE, Agreus L. Psychological illness is commonly associated with functional gastrointestinal disorders and is important to consider during patient consultation: a population-based study. *BMC Med* 2005;3:8.
6. Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol* 2001;96:1998-2004.
7. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry* 1976;128:280-289.
8. Ettema JHM, Arrindell WA. SCL-90: manual for a multidimensional indicator of psycho-pathology (in Dutch). Lisse, Swets & Zeitlinger, 2003:103.
9. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, *et al*. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-1068.

10. Zerbib F, Roman S, Ropert A, des Varannes SB, Pouderoux P, Chaput U, *et al*. Esophageal pH-impedance monitoring and symptom analysis in GERD: a study in patients off and on therapy. *Am J Gastroenterol* 2006;101:1956-1963.
11. Galmiche JP, Clouse RE, Balint A, Cook IJ, Kahrilas PJ, Paterson WG, *et al*. Functional esophageal disorders. *Gastroenterology* 2006;130:1459-1465.
12. Locke GR, Weaver AL, Melton LJ, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004;99:350-357.

3

Maintenance Treatment for GORD:

Residual Symptoms are Associated with Psychological Distress

ABSTRACT

Aim

The aim of this study was to explore determinants of residual reflux symptoms among patients with gastro-oesophageal reflux disease (GORD) despite maintenance treatment with acid suppressive medication (ASM).

Methods

Primary care GORD patients on chronic ASM were classified as symptom-free (55%) or symptomatic (45%) according to the impact of their residual reflux symptoms (QolRad). They were compared with respect to lifestyle (BMI, alcohol, smoking, physical exercise), compliance (daily ASM dosage), disease history, psychological factors (SCL-90) and quality of life (SF-36).

Results

None of the investigated lifestyle factors, nor dosage and disease history were related to residual symptoms. However, symptomatic patients differed from patients with relief on all psychological and quality of life dimensions. In a multiple logistic regression model somatization, hostility, mental health, body pain, as well as gender were independently associated with residual symptoms; the derived ROC curve had an AUC of 0.78.

Conclusions

The majority of GORD patients is symptom-free on chronic ASM; they display a healthy psychological state and high quality of life. Residual symptoms however, are associated with psychological distress and lower quality of life. Recognition of this subgroup might hold the key to improving long-term management of gastro-oesophageal reflux.

INTRODUCTION

Gastro-oesophageal reflux disease (GORD) is a frequent reason for consultation in primary care; on average two new patients visit their general practitioner with reflux symptoms, and three patients require repeat prescription every week [1]. According to current guidelines (NICE, SIGN, CBO), treatment of reflux is directed towards symptom relief, and acid suppressive medication (ASM) is often prescribed on an empirical basis.

ASM treatment results in sustained acid reduction [2] and, thereby, in symptom control in the majority of patients. However, up to 30% of patients remains symptomatic on standard dosages of ASM, and the majority of them even experiences refractory symptoms on higher dosages [3, 4]. Long-term ineffectiveness of ASM pharmacotherapy is a common problem in primary care. Also from an economic perspective as these patients tend to repeatedly utilize healthcare resources by frequent consultations, referrals, diagnostic tests, and repeat prescriptions.

Several factors might contribute to symptom persistence despite treatment. Therapy compliance might play a role; on the long run patients tend to take ASM non-continuously [5] and discontinuity in therapy induces relapses. Secondly, psychological factors are reported to play not only a role in the pathogenesis of GORD [6-8], but also in patients' perception and exacerbation of symptoms [9-11]. Thirdly, lifestyle factors such as smoking, alcohol, and overweight influence symptom severity [12, 13] and could contribute to inadequate symptom control by standard ASM therapy.

The individual contribution of these factors in symptom persistence is not known. In a cross-sectional study in primary care we analyzed determinants of inadequate symptom control in GORD patients on chronic acid suppression. Identification of these characteristics could improve the management of GORD patients with symptoms refractory to standard treatment.

METHODS

Patient selection

Patients between 18 and 75 years of age, on chronic ASM (using at least 180 defined daily dosages (DDD) in the previous year), with a history of GORD or GORD-like symptoms were recruited from primary care practices in the Netherlands after selection through local pharmacies. The general practitioner excluded patients with documented Barrett's oesophagus or oesophagitis grade C/D, acute peptic ulcer disease, dominant irritable bowel syndrome, unstable co-morbidity, and those using

non-steroidal anti-inflammatory drugs. The inclusion characteristics of all patients were used for this study; patients were subsequently included in a randomized trial (assessment of the minimal effective ASM dosage by blinded, patient-controlled dosage adjustment). The University Medical Center Utrecht Ethics Committee approved the study protocol, and all participants provided written informed consent.

Assessments

The patient's medical record was screened for gastrointestinal morbidity, years since the first episode and co-morbidity. Information regarding smoking (yes, no), alcohol use (never/rarely, <3, ≥3 consumptions/day), physical exercise (never/rarely, regularly, at least every week) and body mass index (BMI, kg/m^2) was obtained. At study entry, patients were questioned about the frequency of residual reflux episodes (never, at least monthly, weekly, or daily) and were asked to complete the following questionnaires:

1. Quality of Life in Reflux and Dyspepsia (QolRad)

This instrument monitors disease-related quality of life in patients suffering from reflux; QolRad outcome was shown to reflect treatment response and impact of symptoms [14]; the recall period refers to the last week. It includes 25 items combined into 5 dimensions: emotional distress, sleep disturbance, vitality, food/drink problems, and physical/social functioning. A 7-point scale is used to assess item severity or frequency (1: a great deal/all of the time, 2: a lot/most, 3: a moderate amount/quite a lot, 4: some, 5: a little, 6: hardly any, 7: none). Patients scoring 6 or higher on all dimensions were considered symptom-free, patients scoring lower than 6 on at least one dimension as symptomatic.

2. Symptom Check List 90 (SCL-90)

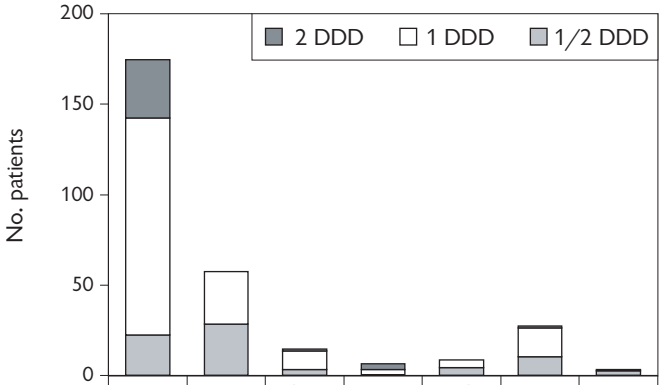
This validated questionnaire reflects psychological symptom state [15, 16]. Using 90 items answered on a 5-point scale, it covers 8 dimensions of mental health: anxiety, phobic anxiety, depression, somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility, and sleeping problems. A high score indicates the presence of a psychological symptom or psychiatric diagnosis.

3. SF-36 health survey

This 36-question survey measures generic quality of life on 8 dimensions [17, 18]: physical functioning, role limitations due to physical health problems, body pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and general mental health. Crude scores are converted to a 0-100 scale, with higher scores indicating higher levels of health or well-being.

Data analysis

Descriptive statistics (mean and SD) and additional analyses were calculated using SPSS version 14.0. In case of missing values in the questionnaires, the mean of the completed items in one dimension was imputed for the missing item, provided that more than 80% (SCL-90, [16]) or more than 50% (QolRad and SF-36, [19]) of the items in that dimension were completed. Mean values were compared using the Students t-test, and differences between dichotomous variables with the χ^2-test; two-sided p-values of <0.05 were considered significant. SCL-90 and SF-36 scores were also dichotomized, simplifying the interpretation of modeling. For the SCL-90, a psychological symptom was considered present when scored above the Dutch population average (gender-stratified, [16]), and for the SF-36, health was considered impaired when scored below the Dutch average (age-stratified, [17]); 95% confidence limits and 2-tailed p-values were calculated for the odds ratios. Multivariate logistic regression analysis was carried out using determinants with p-values of <0.1. Backward-stepwise logistic modeling was performed with a cut-off value of 0.05 for expulsion from the model. Determinants surviving in the final model were tested for their combined predictive value towards identification of symptomatic patients using the area under the receiver operating characteristic (ROC) curve [20].



	ome	pan	lan	eso	rab	ran	cim
2 DDD	32		1	3		1	
1 DDD	119	29	10	3	4	16	1
1/2 DDD	22	28	3		4	10	2

Figure 1: Medication and dosage used by the patients.
DDD: defined daily dosage, ome: Omeprazole, pan: Pantoprazole, lan: Lansoprazole, eso: Esomeprazole, rab: Rabeprazole, ran: Ranitidine, cim: Cimetidine.

RESULTS

A total of 288 patients with a history of GORD or GORD-like symptoms on chronic ASM were included in the study (mean age 57 years, 56% male). Considering the gastrointestinal problem that initiated use of ASM, 54% of patients had a documented history of oesophagitis (35% grade A, 19% grade B), 40% of GORD, reflux or pyrosis, and 6% of hiatus hernia. Patients experienced their first episode on average 7 years earlier, and used a mean of 350 DDD in the year preceding the study. The medication and dosages they used are shown in Figure 1; almost 90% used a proton pump inhibitor (PPI) and the vast majority Omeprazole 20 mg daily.

Residual reflux symptoms were investigated by analyzing their impact (QolRad) and frequency (Table 1). No or hardly any impact of symptoms (all QolRad dimensions ≥6) was reported by 158 patients (55%), which corresponded to a low frequency of episodes; 93% of them reported no or monthly episodes. A little or more severe impact of reflux symptoms despite treatment (at least one QolRad dimension <6) was reported by 130 patients (45%). Mainly food and drink behavior/tolerance, vitality and sleep disturbance were reported to be affected by incomplete relief, and 70% of these patients indeed reported daily or weekly episodes. The vast majority of patients classified as having residual symptoms but expressing no or monthly episodes, score below 6 on the QolRad food/drink dimension; reflux episodes can be omitted by avoiding certain food, eating less than usual, and/or a decreased appetite.

Table 1: Impact and frequency of residual reflux symptoms.

	Residual symptoms* (n=130)	Symptom-free# (n=158)
Frequency of episodes (%)		
Never	8	62
Monthly	22	31
Weekly	46	6
Daily	24	1
QolRad dimension (mean ± SD)		
Emotional distress	5.9 ± 1	7 ± 0.1
Sleep disturbance	5.5 ± 1.2	6.9 ± 0.2
Food/drink problems	5 ± 1	6.8 ± 0.3
Physical/social functioning	6 ± 1	6.9 ± 0.1
Vitality	5.1 ± 1.1	6.8 ± 0.3

* At least one QolRad dimension <6, # all dimensions ≥6.

The subdivision based on impact of residual symptoms was used to investigate determinants of inadequate symptom control. Relatively more female patients and patients not drinking alcohol expressed residual symptoms under ASM therapy (p=0.02 and 0.01, respectively, Table 2). In univariate analysis, the age of the patient, BMI, the annually used DDD (compliance), use of PPIs or histamine-2-receptor antagonists, years since first episode, history of oesophagitis, co-morbidity, smoking and physical exercise were not related to inadequate symptom control (Table 2). Patients with residual reflux symptoms scored significantly higher on all psychological dimensions ($p<0.0001$), except for phobic anxiety. They also scored lower on all dimensions of generic quality of life ($p<0.003$), except for role limitations due to emotional problems (Figure 2).

All variables were dichotomized and analyzed in multivariate analysis; somatization, hostility, general mental health, body pain and gender were independently associated with residual symptoms (Table 3). Based on these five determinants, 72% of patients could correctly be classified into the residual symptoms- and complete relief groups. The area under the ROC-curve, quantifying the usefulness of the model to allocate patients to residual symptoms, was 0.78.

Table 2: General, dosage, and lifestyle characteristics of patients with and without residual symptoms.

Variables		Residual symptoms (n=130)	Symptom-free (n=158)	p-value of difference
Gender (% male)		49	62	0.02
Age (years)		57 ± 10.5	56.5 ± 10.7	0.7
BMI		28.2 ± 5	27.1 ± 4.2	0.06
DDD of ASM		346 ± 164	352 ± 161	0.7
Time since first episode (years)		7.5 ± 5	6.7 ± 4.6	0.16
Medication (% H2RA)		14	8	0.12
Oesophagitis history (%)		54	54	1
Co-morbidity (number)		1.1 ± 1	1.2 ± 1	0.4
Smoking (% yes)		21	21	1
Alcohol (%)	never, rarely	55	38	0.01
	<3/day	40	55	
	≥3/day	5	7	
Physical exercise (%)	never, rarely	11	9	0.07
	regularly	13	6	
	at least every	76	85	

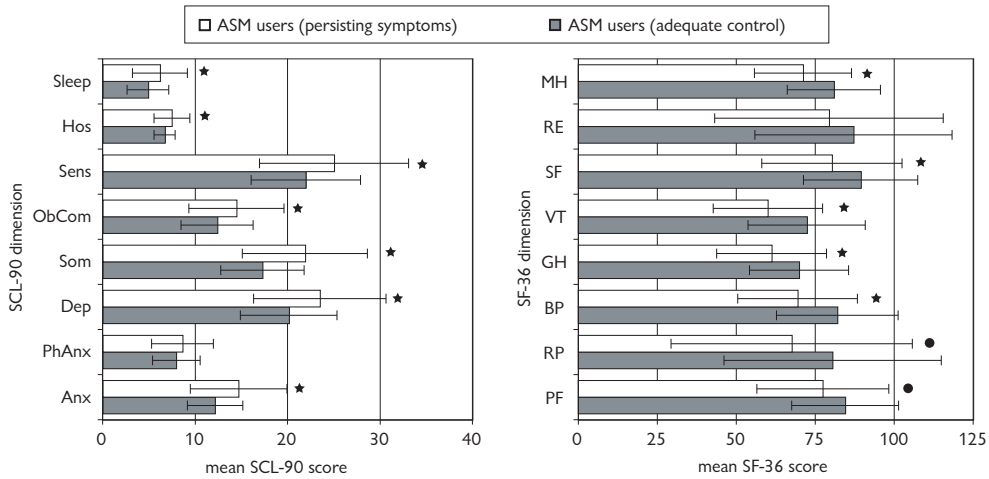


Figure 2: Psychological state and generic quality of life of patients with and without residual symptoms.
Means and SDs of SCL-90 and SF-36 dimensions are shown. Anx: anxiety, PhAnx: phobic anxiety, Dep: depression, Som: somatization, ObCom: obsessive-compulsive behavior, Sens: interpersonal sensitivity, Hos: hostility, Sleep: sleeping problems, PF: physical functioning, RP: role limitations due to physical health problems, BP: body pain, GH: general health perception, VT: vitality, SF: social functioning, RE: role limitations due to emotional problems, MH: general mental health. * $p<0.0001$, • $p<0.005$.

DISCUSSION

This cross-sectional study demonstrates that the majority of patients with a history of GORD and GORD-like symptoms using chronic ASM is symptom-free (55%), experiences an above-average quality of life, and displays a normal psychological state. However, those with residual or recurrent symptoms despite treatment represent a large subgroup (45%) with relatively high psychological distress and a significantly lower generic quality of life.

In our patient population the subgroup with residual reflux symptoms was larger than reported by others (30%) [4]. These studies assessed symptom relief about four weeks after initiation of a daily dosage of ASM. We determined relief at six months up to several years after initiation of therapy, and allowed variable dosages. Therefore, incomplete relief in our population might also have been caused by exacerbation of the gastrointestinal disorder, by relapses, or reduced therapy compliance.

Prognostic studies identified disease-related- and psychological indicators for treatment success in GORD; patients without adequate relief were likely to have non-erosive reflux disease [4, 21], and showed decreased psychological well-being, particularly through anxiety, depression, and decreased vitality [22, 23]. Though we

Table 3: Determinants of residual symptoms in GORD patients on ASM.

	OR	CI (95%)	p-value
General and lifestyle			
Gender (f/m)	1.7	1.1 - 2.9	0.03
	1.8	**1 - 3**	**0.04**
Age (>55/≤55)	1.2	0.7 - 1.9	0.6
Overweight (BMI ≥25/<25)	1.6	0.9 - 2.7	0.09
Obesity (BMI ≥30/<30)	1.5	0.8 - 2.6	0.2
DDD (<360/≥360)	1.2	0.7 - 2	0.5
Years since 1st episode (<5/≥5)	0.8	0.5 - 1.3	0.4
Medication (H2RA/PPI)	1.9	0.9 - 4.2	0.1
Oesophagitis history (y/n)	1	0.6 - 1.6	1
Co-morbidity (y/n)	0.8	0.5 - 1.4	0.5
Alcohol (y/n)	0.5	0.3 - 0.8	0.005
Smoking (y/n)	1	0.5 - 1.8	1
Phys exercise (n/y)	1.2	0.5 - 2.9	0.7
Psychological factors			
Anxiety	2.8	1.7 - 4.8	<0.0001
Phobic anxiety	1.6	0.9 - 2.7	0.1
Depression	3.2	1.9 - 5.4	<0.0001
Somatization	4.2	2.4 - 7.4	<0.0001
	2.8	**1.6 - 5.1**	**0.001**
Obsessive-compulsive behavior	2.1	1.3 - 3.4	0.003
Interpersonal sensitivity	2.4	1.4 - 4.2	0.001
Hostility	4.1	2.2 - 7.7	<0.0001
	2.9	**1.5 - 5.5**	**0.001**
Sleep	2.4	1.5 - 4	0.0004
General health aspects			
Physical functioning	1.3	0.8 - 2.2	0.3
Limitations, physical problem	2.2	1.3 - 3.8	0.004
Body pain	3.2	1.9 - 5.4	<0.0001
	1.8	**1 - 3.1**	**0.04**
General health perception	2.4	1.5 - 4	0.0005
Vitality	2.8	1.7 - 4.7	<0.0001
Social functioning	2.3	1.4 - 3.9	0.002
Limitations, emotional problem	2	1.1 - 3.7	0.03
General mental health	4.2	2.5 - 7.1	<0.0001
	2.4	**1.4 - 4.2**	**0.002**

Variables were dichotomized as indicated, or as described in Methods. Bold variables appear to be independently associated with persisting symptoms in a multivariate model (alcohol was not included in the model). OR: odds ratio, CI: confidence interval (bold: adjusted OR/CI).

included a history of oesophagitis in our analysis, no objectively confirmed diagnosis or disease history was available for all patients. This is common practice in primary care, where the majority of patients with GORD-like symptoms is empirically treated and not subjected to diagnostic testing.
We investigated several patient-related characteristics as possible determinants for inadequate symptom relief. It appeared that especially psychological factors were strongly associated. Two psychological features (somatization and disturbed mental health) appeared highly indicative; 73% of patients displaying these two items was indeed symptomatic, whereas 85% of patients with normal values reported complete relief (data not shown). We found no correlation between residual symptoms and the volume of ASM used, which we included as a measure for compliance.

Over decades ample evidence has accumulated that psychological factors are associated with gastrointestinal disease. Recently, in community samples with symptomatic subjects a direct relationship was demonstrated [6, 8]. Initially we observed that the psychological state of our patient group was comparable to the average of the Dutch population (*chapter 2.3*). Upon further analysis we noticed that based on the adequacy of symptom relief, this apparently heterogenic group can be divided into a psychologically distressed and a mentally healthy subgroup.
Though our study adds to the evidence that for the majority of patients psychological distress is not part of the gastrointestinal disorder itself but is directly related to its symptoms, the causal direction can however not be determined; does psychological distress result in symptomatology, or do symptoms result in psychological distress? A vicious circle in which these two pathways reinforce each other can be envisioned. Psychological state and stress have been shown to play a role in symptom perception and exacerbation. Dissociation between subjective symptom rating and objectively measured reflux was observed in subjects with higher levels of anxiety and hysteria [24] and during stress [11], and sustained life stress increased heartburn severity but not its frequency [10]. These data indicate that psychological state and stress have an impact on perception, rather than on causal mechanisms. Therefore, due to emotional instability, patients could become hypervigilant resulting in perception of symptoms. In addition to psychological hypersensitivity, it is hypothesized that the hyperactive locus ceruleus of mentally distressed patients physiologically enhances the awareness of symptoms [25]. Exacerbation and increased symptom perception might then result in more elevated levels of psychological distress (anxiety, depression, vitality, pain), which enhances symptoms even further. On the other hand, symptom-induced psychological distress could normalize as an additional result of successful ASM therapy.

Based on this model, treatment of symptomatic ASM-using GORD patients could be improved through more effective acid suppression, and through psychological intervention. First, compliance, timing and dosage should be evaluated. Poor compliance can be a cause for incomplete therapy success; only 55% of GORD patients takes their PPI once daily as prescribed [5]. For maximal efficacy PPIs should be taken approximately 30 minutes prior to a meal [26, 27]; sub-optimal dosage timing was highly prevalent in primary care patients with poorly controlled GORD [28]. Especially in primary care, limited benefits of a double dosage on healing rates and relief of heartburn were reported [29-31].

Psychological distress should additionally be evaluated in patients with persisting symptoms. In primary care, shorter and more accentuated methods than the SCL-90 can be used: the BSI [32] or 4DSQ [33]. If psychological distress is identified, additional therapy should be considered. Both pharmacotherapy (tricyclics or selective serotonin reuptake inhibitors), as well as psychological interventions (cognitive-behavioral therapy, psychotherapy and relaxation training) have been suggested to be beneficial in dyspepsia management [34-38]. In conclusion, evaluation and management of psychological distress might be supportive in the treatment of residual or recurrent symptoms in GORD patients already on chronic acid suppressive therapy.

REFERENCES

1. Hurenkamp GJ, Grundmeyer HG, Bindels PJ, Tytgat GN, van der Hulst RW. How do primary care physicians use long-term acid suppressant drugs? A population-based analysis of Dutch general practices. *J Fam Pract* 2002;51:241-245.
2. Van Pinxteren B, Numans ME, Bonis PA, Lau J. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev* 2006;3:CD002095.
3. 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;98:1940-1944.
4. 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.
5. 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.

6. Ålander T, Svardsudd K, Johansson SE, Agreus L. Psychological illness is commonly associated with functional gastrointestinal disorders and is important to consider during patient consultation: a population-based study. *BMC Med* 2005;3:8.
7. Baker LH, Lieberman D, Oehlke M. Psychological distress in patients with gastroesophageal reflux disease. *Am J Gastroenterol* 1995;90:1797-1803.
8. Locke GR, Weaver AL, Melton LJ, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. *Am J Gastroenterol* 2004;99:350-357.
9. Johnston BT, Lewis SA, Collins JS, McFarland RJ, Love AH. Acid perception in gastro-oesophageal reflux disease is dependent on psychosocial factors. *Scand J Gastroenterol* 1995;30:1-5.
10. Naliboff BD, Mayer M, Fass R, Fitzgerald LZ, Chang L, Bolus R, Mayer EA. The effect of life stress on symptoms of heartburn. *Psychosom Med* 2004;66:426-434.
11. Wright CE, Ebrecht M, Mitchell R, Anggiansah A, Weinman J. The effect of psychological stress on symptom severity and perception in patients with gastro-oesophageal reflux. *J Psychosom Res* 2005;59:415-424.
12. Kaltenbach T, Crockett S, Gerson LB. Are lifestyle measures effective in patients with gastroesophageal reflux disease? An evidence-based approach. *Arch Intern Med* 2006;166:965-971.
13. Jacobson BC, Somers SC, Fuchs CS, Kelly CP, Camargo CA. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006;354:2340-2348.
14. Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol* 2001;96:1998-2004.
15. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry* 1976;128:280-289.
16. Ettema JHM, Arrindell WA. SCL-90: Manual for a multidimensional indicator of psycho-pathology (in Dutch). Lisse, Swets & Zeitlinger, 2003, pp 97, 103.
17. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-1068.
18. Ware JE, Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, Brazier J, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M. The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;51:1159-1165.

19. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey Manual and Interpretation Guide. Boston, New England Medical Center, The Health Institute, 1993, pp 6:16.
20. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29-36.
21. Dean BB, Gano AD, Knight K, Ofman JJ, Fass R. Effectiveness of proton pump inhibitors in nonerosive reflux disease. *Clin Gastroenterol Hepatol* 2004;2:656-664.
22. Lind T, Havelund T, Carlsson R, Anker-Hansen O, Glise H, Hernqvist H, Junghard O, Lauritsen K, Lundell L, Pedersen SA, Stubberod A. Heartburn without oesophagitis: efficacy of omeprazole therapy and features determining therapeutic response. *Scand J Gastroenterol* 1997;32:974-979.
23. Wiklund I, Carlsson R, Carlsson J, Glise H. Psychological factors as a predictor of treatment response in patients with heartburn: a pooled analysis of clinical trials. *Scand J Gastroenterol* 2006;41:288-293.
24. Johnston BT, Lewis SA, Love AH. Psychological factors in gastro-oesophageal reflux disease. *Gut* 1995;36:481-482.
25. Van Oudenhoven L, Demyttenaere K, Tack J, Aziz Q. Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004;18:663-680.
26. 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;14:1267-1272.
27. 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;91:1532-1538.
28. Gunaratnam NT, Jessup TP, Inadomi J, Lascewski DP. Sub-optimal proton pump inhibitor dosing is prevalent in patients with poorly controlled gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2006;23:1473-1477.
29. Bate CM, Booth SN, Crowe JP, Hepworth-Jones B, Taylor MD, Richardson PD. Does 40 mg omeprazole daily offer additional benefit over 20 mg daily in patients requiring more than 4 weeks of treatment for symptomatic reflux oesophagitis? *Aliment Pharmacol Ther* 1993;7:501-507.
30. Meineche-Schmidt V. Empiric treatment with high and standard dose of omeprazole in general practice: two-week randomized placebo-controlled trial and 12-month follow-up of health-care consumption. *Am J Gastroenterol* 2004;99:1050-1058.
31. Moretzsohn LD, Brito EM, Reis MS, Coelho LG, Castro LP. Assessment of effectiveness of different dosage regimens of pantoprazole in controlling symptoms and healing esophageal lesions of patients with mild erosive esophagitis. *Arq Gastroenterol* 2002;39:123-125.

32. Derogatis LR, Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med* 1983;13:595-605.
33. Terluin B, van Marwijk HW, Ader HJ, de Vet HC, Penninx BW, Hermens ML, van Boeijen CA, van Balkom AJ, van der Klink JJ, Stalman WA. The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization. *BMC Psychiatry* 2006;6:34.
34. Clouse RE, Lustman PJ. Use of psychopharmacological agents for functional gastrointestinal disorders. *Gut* 2005;54:1332-1341.
35. Otaka M, Jin M, Odashima M, Matsuhashi T, Wada I, Horikawa Y, Komatsu K, Ohba R, Oyake J, Hatakeyama N, Watanabe S. New strategy of therapy for functional dyspepsia using famotidine, mosapride and amitriptyline. *Aliment Pharmacol Ther* 2005;21 Suppl 2:42-46.
36. Schmulson MJ, Valdovinos MA. Current and future treatment of chest pain of presumed esophageal origin. *Gastroenterol Clin North Am* 2004;33:93-105.
37. Kamolz T, Granderath FA, Bammer T, Pasiut M, Pointner R. Psychological intervention influences the outcome of laparoscopic antireflux surgery in patients with stress-related symptoms of gastroesophageal reflux disease. *Scand J Gastroenterol* 2001;36:800-805.
38. Donald-Haile J, Bradley LA, Bailey MA, Schan CA, Richter JE. Relaxation training reduces symptom reports and acid exposure in patients with gastroesophageal reflux disease. *Gastroenterology* 1994;107:61-69.

4

Pharmacological Dependency in Chronic Treatment of GORD: a Randomized Controlled Clinical Trial

ABSTRACT

Background

Despite evidence for overuse of acid suppressive medication for GORD, transfer to non-continuous therapy after long-term treatment proves difficult.

Aim

To quantify the effect of blinded dosage reduction after long-term therapy on symptom control and quality of life, while assessing pharmacological and placebo needs.

Methods

Primary care patients with a history of GORD and long-term treatment were randomized to daily placebo with Pantoprazole rescue, or daily Pantoprazole with placebo rescue (upon relief after 4 weeks Pantoprazole 20 mg). The number of rescue tablets, symptom control and generic quality of life were analyzed.

Results

19% of patients terminated treatment, 33% managed with 2 - 6 tablets/week, 38% needed a daily dosage, and 10% more than a daily dosage on the longer run. At these final dosages, symptom control and quality of life were dosage-independent, and furthermore equal to values of patients on fixed daily Pantoprazole. A temporal decrease in well-being was seen in 24% of patients.

Conclusion

A significant placebo response is apparent in long-term users of acid suppressive medication and pharmacological dependency is overestimated. Despite their history of long-term treatment, the majority of GORD patients can be switched from daily to on-demand treatment without impairing symptom control and quality of life.

INTRODUCTION

Acid suppressive medication (ASM) is the most effective therapy for patients with gastro-oesophageal reflux disease (GORD) in short- as well as in long-term treatment [1, 2]. It is consistently demonstrated that proton pump inhibitors (PPI) are being overprescribed, and consequently many patients with GORD symptoms are on ASM therapy without an appropriate indication [3, 4]. Longstanding maintenance therapy for GORD symptoms has become standard practice, in which both physicians and patients played their role. Following guidelines or advertisement of pharmaceutical companies, a positive PPI response is erroneously accepted as a diagnosis of GORD without further proof, resulting in superfluous prescription. Patients with oesophagitis grade C/D have a recommended pharmacological indication for continuous acid suppression. In patients without this evidence-based indication high therapy satisfaction and a considerable placebo effect is apparent. Placebo effects of 30 to 50% of the magnitude of PPI treatment have been reported in initial treatment [5, 6]. This placebo effect is further accentuated by relapses [7] and rebound hyperacidity after therapy cessation [8].

There is compelling evidence that chronic use of ASM for GORD symptoms can be reduced by carefully reconsidering the reason for prescription. Research demonstrates that up to 80% of presumably GORD patients on continuous PPI treatment can be stepped down to less intensive therapy: dosage reduction, on-demand-, or intermittent therapy [9-11].

Symptom control and quality of life are the most relevant determinants of treatment success in patients with GORD symptoms [12, 13]. Although dosage reduction among long-term treated patients seems possible, the impact of transfer to on-demand treatment in comparison to continuous daily therapy on short- and longer-term symptom control and quality of life has not been investigated yet. Randomized, placebo-controlled studies compared on-demand PPI use with on-demand placebo use [10, 11]; no comparison with daily treatment was made and furthermore, patients in these trials were aware of their dosage reduction.

In primary care there is a large group of patients adequately relieved from GORD symptoms by using daily dosages of ASM and not very willing to experiment with dosage reduction. Dosage reduction is promoted by health care insurers for budgetary reasons and by physicians to prevent unnecessary use [4]. More evidence is needed to show that dosage reduction by GORD patients is possible without impairing disease-related or generic quality of life. We therefore investigated the impact of blinded, patient-controlled dosage reduction on symptom control and quality of life in GORD patients on longstanding ASM in comparison to daily therapy. Furthermore, we evaluated pharmacological and placebo aspects of their medication dependency.

METHODS

Study design

Multicentre, randomized, double-blind, parallel-group trial.

Setting

Patients were enrolled from 26 general practices in the central and eastern regions of the Netherlands. The study was conducted between March 2004 and September 2006 in accordance with the Declaration of Helsinki, following Good Clinical Practice. The protocol was approved by the Ethics Committee of the University Medical Center Utrecht, and all participants provided written informed consent. Trial was registered at US National Institutes of Health, ClinicalTrials.gov: NCT00161096.

Participants

Patients on continuous ASM (PPI or histamine-2-receptor antagonist) for at least 6 months were selected from prescription records. The general practitioner screened for in- and exclusion criteria, and invited patients for participation. *Inclusion criteria:* age between 18 and 75 years, history of GORD or GORD-like symptoms, ASM consumption of 180 defined daily dosages (DDD) or more in the previous year (definition of chronic use in the Netherlands). *Exclusion criteria:* documented history of Barrett's oesophagus, oesophagitis C/D, a gastric hypersecretory condition, acute peptic ulcers, pyloric stenosis, severe or unstable co-morbidity, alarm symptoms, and use of systemic glucocorticoids, non-steroidal anti-inflammatory drugs, and Cox-2 inhibitors.

Trial procedure

At inclusion patients were switched to daily Pantoprazole 20 mg (Nycomed BV, The Netherlands) during a 4 weeks run-in period. Upon symptom control after run-in, they were randomized to either daily placebo treatment with Pantoprazole 20 mg as rescue medication, or to daily Pantoprazole with placebo rescue for 13 weeks. Patients were instructed to routinely take one tablet per day from the daily-container, and in case of inadequate symptom control to use one tablet daily from the rescue-container. No other ASM or antacids were allowed during the study.

Randomization, blinding

Randomization was performed in sets of 6 (daily Pantoprazole to daily placebo: 2 to 4) using a computer-generated list, according to which an external party generated sealed sequentially numbered identical containers. Sets were sent to the general

practitioners, where the nurse allocated the next available number of the set on entry into the trial. We entered twice as many patients in the daily placebo group as they titrated their dosage, whereas the daily Pantoprazole group was only needed as a control and to blind the study.
Study was performed double-blind; after completion of the study unblinded data were analyzed.

Measurements

Participants were supervised by research nurses. Information regarding gastrointestinal morbidity, ASM in use (brand, dosage, DDD), smoking (yes/no), alcohol use, and for the BMI (kg/m^2) was obtained. Patients were asked to complete the following questionnaires:
Quality of life in reflux and dyspepsia (QolRad)
This instrument monitors disease-related quality of life in patients suffering from reflux; QolRad outcome was shown to reflect treatment response and impact of symptoms [14]. It includes 25 items combined into 5 dimensions: emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning. A 7-point scale is used to assess item severity or frequency (1: a great deal/all of the time, 2: a lot/most, 3: a moderate amount/quite a lot, 4: some, 5: a little, 6: hardly any, 7: none).
SF-36 health survey
This 36-questions survey measures generic quality of life on 8 dimensions [15-17]: physical functioning, role limitations due to physical health problems, body pain, general health perception, vitality, social functioning, role limitations due to emotional problems and general mental health. Scores are linearly converted to a 0-100 scale; higher scores indicate higher levels of health or well-being.

Follow-up

Participants visited the nurse at week 4, 10 and 17, or soon after premature study termination for a final visit; SF-36 and QolRad questionnaires were repeated, study medication was returned and counted (compliance for daily, and use of rescue medication), and new medication was dispensed. At week 5, participants were phoned to inform about their well-being. As patients, on their own initiative, reported the randomization arm they believed to participate in, this was registered without discussion.

Outcome measures

Primary outcome was the volume of rescue medication per week; three dosage groups were created: 0 - <2 tablets/week ((almost) quitting treatment), 2 - <6/week (substantial reduction), 6 - 7/week (ongoing daily treatment). Secondary outcomes were final adjusted dosage and reported symptom control and generic quality of life (in randomization arms, as well as in dosage groups).

Data analysis

We did an intention to treat (ITT) analysis among patients adequately treated with daily Pantoprazole in the run-in, representing stable long-term treated patients. Results of patients leaving the study after randomization for other reasons than inadequate relief were used in the analyses according to data at their final visit. Patients who discontinued for inadequate relief (unable to adjust a satisfying dosage), were classified as needing a daily dosage or more; at study discontinuation patients also received this advice. Of these patients, no post-study data were available for the ITT analysis on well-being at this advised final dosage; therefore, QolRad and SF-36 values after 4 weeks of daily Pantoprazole were imputed, as these most likely represent well-being on the final dosage.
Data were collected on case report forms using Teleform. Descriptive statistics and statistical analyses were calculated using SPSS version 14.0. Baseline characteristics, SF-36 and QolRad scores, and their changes were compared with the Student's t- and χ^2-tests. Differences between the dosage groups were evaluated by one-way ANOVA. All testing was two-tailed, with $p<0.05$ defined as significant.

RESULTS

Trial description

A total of 288 patients were included in the study; their characteristics are summarized in Table 1. Prior to study entry 90% used a PPI and 10% a H2RA. All patients were transferred to daily Pantoprazole 20 mg. During this run-in period 85 patients (29.5%) discontinued the study (Figure 1), 70 of them for inadequate relief of symptoms on the study medication (82.4%). Of the remaining 203 patients, 141 were randomized to daily placebo with Pantoprazole 20 mg as rescue; these patients blindly titrated their need for PPI. 62 patients were randomized to daily Pantoprazole 20 mg with placebo rescue; they used active medication daily. Randomization was balanced (Table 1).
In the daily Pantoprazole arm 52 patients completed the study, 5 patients (8%) discontinued for inadequate relief, and 5 for other reasons (Figure 1). In the daily

Table 1: Patient characteristics of the total enrolled and randomized population.

		randomized population	
	*total enrolled	#daily Panto	#daily placebo
Characteristics	n=288	n=62	n=141
General (mean/%)			
Age	57	59	56
Body mass index	27.6	28.1	27.4
Yearly dosage (DDD)	350	311	330
Years on ASM	7.3	7.2	7.4
Gender (% male)	56	55	60
Smoking (% yes)	21	16	21
Alcohol (% yes)	54	47	58
QolRad (mean)			
Emotional distress	6.5	6.7	6.7
Sleep disturbance	6.3	6.5	6.5
Food/drink problems	6	6.2	6.2
Phys/soc functioning	6.5	6.6	6.6
Vitality	6.1	6.2	6.2
SF-36 (mean)			
Physical functioning	81.3	79.3	82.8
Social functioning	85.3	84.3	89
Role lim physical	74.7	77.8	79.3
Role lim emotional	83.6	87.5	87.3
Mental health	76.5	76.2	79.3
Vitality	66.7	67.8	68.4
Body pain	76.3	79.9	81.3
General health percep	66.0	66.4	68.3

* At inclusion, # comparison for general characteristics at inclusion, and for QolRad and SF-36 values at randomization.

placebo arm, 94 patients successfully completed the study, 34 patients (24%) discontinued for inadequate relief and 13 for other reasons.

Use of rescue medication

Use of rescue medication was analyzed for patients who managed on the study regime (n=57 and n=107 in both arms), and separately for patients who failed to adjust a satisfying dosage and consequently discontinued for inadequate relief (n=5 and

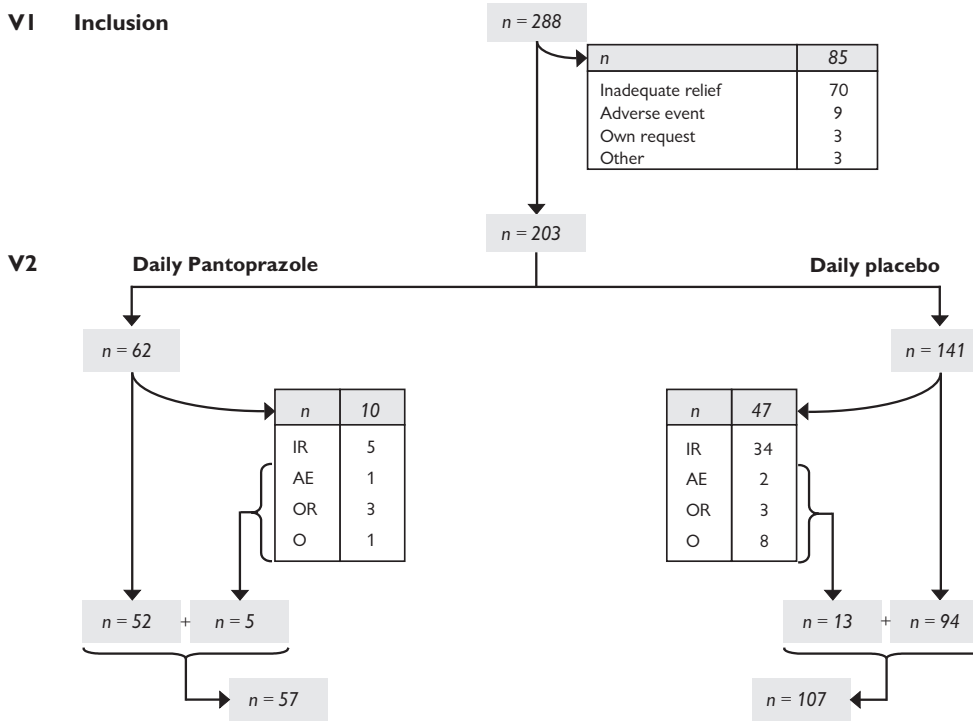


Figure 1: Trial design.
Patients leaving the study are shown with reasons for discontinuation.

n=34). Of patients who managed on the study regime in the daily placebo arm (n=107), 34 persisted in a daily 20 mg PPI dosage, 46 reduced their dosage, whereas 27 used less than 2 Pantoprazole tablets weekly. In the daily Pantoprazole arm 91% (52/57) used less than 2 placebo tablets per week (Figure 2).

Of patients discontinuing for inadequate relief in the placebo arm (n=34), 3 used 0 - <2, 17 2 - <6, and 14 6 - 7 Pantoprazole tablets per week. Patients using 6 - 7 PPI tablets without experiencing relief (14 of those randomized to daily placebo, 9.9%) probably need more than a daily dosage for symptom control on the longer run. A similar percentage was found in the Pantoprazole arm, where 8% (5/62) discontinued for inadequate relief despite their daily PPI dosage.

Pharmacological dependency

When all patients randomized to daily placebo were considered (ITT), 19.2% of chronic ASM users stopped treatment, 32.6% switched to an on-demand regime, 38.3% needed a daily dosage, whereas 9.9% needed more than a daily dosage on the longer

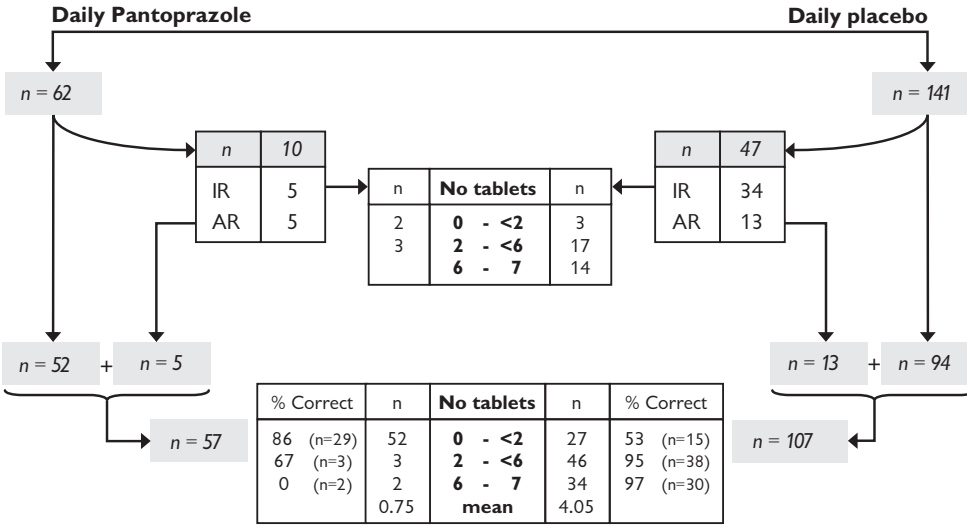


Figure 2: Use of rescue medication.
The numbers of patients per dosage group are shown (n). Furthermore, the percentages of patients with a correct idea about the randomization arm they participated in are indicated (% correct), together with the numbers of patients who expressed this idea. IR: inadequate relief, AR: all other reasons.

run (Table 2). In this calculation, patients discontinuing with inadequate relief and only using 0 - <6 PPI tablets per week were classified as needing a daily dosage (3+17, Figure 2); their mean QolRad score after the run-in of 6.4 shows that this was legitimate.

These 141 patients entered the study using 6.3 DDD per week, whereas during the study symptom control was achieved at a mean of 5.38 tablets of Pantoprazole 20 per week (Table 2), which equals 2.7 DDD, giving a reduction of 57% (20 mg of Pantoprazole is defined as 0.5 DDD). An alterative way to calculate reduction is consumption of 150 mg weekly prior to the study (mg of H2RA standardized) and 108 mg during the study, resulting in a reduction of 28%.

Placebo satisfaction

About 20% of formerly chronic users became satisfied on daily placebo with hardly any PPI medication (0.7 tablet/week). About half of these patients believed they were participating in the daily Pantoprazole arm; these patients can be regarded as highly placebo responsive. In the other two dosage groups only 5 and 3% expressed the wrong arm (Figure 2).

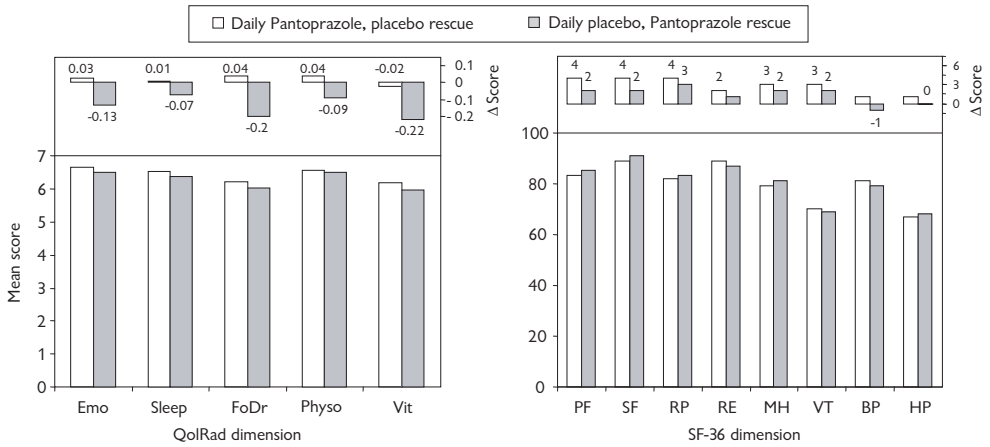


Figure 3: Self-adjusted versus fixed PPI use; symptom control and quality of life.
Patients on daily Pantoprazole (n=62) were compared to patients adjusting their dosage (n=141) with respect to QolRad and SF-36 values at the final dosage; changes (Δ) from randomization to the final state are shown enlarged in the upper panels. Emo: emotional distress, Sleep: sleep disturbance, FoDr: food/drink problems, PhySo: physical/social functioning, Vit: vitality. PF: physical functioning, SF: social functioning, RP: role limitations due to physical problems, RE: role limitations due to emotional problems, MH: mental health, VT: vitality, BP: body pain, HP: health perception.

A fixed versus self-adjusted dosage: symptom control and quality of life

In the daily placebo arm, 24% of patients was unable to adjust a satisfying dosage or was no longer relieved by a daily dosage (8% in the daily Pantoprazole group). Their mean QolRad score at premature study discontinuation of 5.5, with decreases of 0.6 to 1 per dimension, was illustrative for the experienced lack of symptom relief (for all dimensions: $p<0.006$). Generic quality of life decreased as well with significant values for body pain and general health perception ($p=0.02$). In a shared decision, these patients returned to a daily dosage or more; well-being scores at this final dosage were not available. As it can be expected that symptom control will soon be restored upon return to a daily dosage or more, values after 4 weeks on daily Pantoprazole were

Table 2: Pharmacological dependency: final dosages.

tablets/week	n	percentage (%)	Panto 20/week
>7	14	9.9	14 [1]
6 - 7	3+17+34	38.3	6.5 [2]
2 - <6	46	32.6	4.2 [2]
0 - <2	27	19.2	0.7 [2]
	141	100	5.38 (=2.7 DDD)

[1] Set at 2 per day, [2] derived from dosage groups.

Table 3: Different adjusted dosages of PPI medication; comparison of gastrointestinal symptom control.

dosage group	QolRad final (mean)	ΔQolRad total	sleep	food/drink	vitality
0 - <2 (n=27)	6.2	-0.3*	-0.3*	-0.3	-0.5*
2 - <6 (n=46)	6.3	-0.3*	-0.2*	**-0.5***	**-0.6***
6 - 7 (n=34)	6.3	+0.1*	**+0.3***	+0.1*	+0.2*

Only significant QolRad changes during the randomized phase are shown, * $0.01 \leq p < 0.05$. Bold means significant change when tested for no difference (against 0).

used for these patients in the analysis of residual reflux symptoms and generic quality of life at the final dosage (ITT).

At the final dosages for all randomized patients, neither QolRad and SF-36 values, nor patient-specific changes of these variables from randomization up to the final state differed significantly between the two arms (Figure 3). This equal patient satisfaction was achieved at a final dosage of 5.4 tablets per week by patients in the daily placebo group, which is significantly less than 7.6 tablets by patients in the daily Pantoprazole group ($p<0.001$).

Self-adjusted dosage of Pantoprazole: symptom control and quality of life

Symptom control and generic quality of life were further evaluated for patients who adjusted their dosage during the study. Neither final QolRad values (Table 3), nor generic quality of life (not shown) differed significantly between the dosage groups. Yet, small differences were found for patient-specific changes in the QolRad sleep, food/drink and vitality dimensions during the randomized phase (Table 3); slight increases were seen in patients taking daily Pantoprazole, whereas small decreases were seen in patients taking less. However, no differences were found between patients using 0 - <2 and 2 - <6 tablets per week, and furthermore, when dosage groups were tested for changes in QolRad dimensions against 0, only the food/drink and vitality dimensions of the 2 - <6 group decreased significantly.

DISCUSSION

Principal findings

This is the first blinded study where pharmacological dependency for ASM was assessed in patients on longstanding chronic therapy, and where symptom control and quality of life were related to a blindly adjusted dosage. Less than 50% of chronic

users depended on a daily dosage or more, and a significant placebo satisfaction was apparent. A 30% reduction in medication use was obtained with a temporal reduction of symptom control and generic quality of life in a minority of patients.

Background

Initially, PPIs were only approved for erosive oesophagitis, but are now widely used for treatment of more prevalent endoscopy-negative reflux disease. In primary care a large group of GORD patients uses ASM without evidence-based indication for their prolonged and high usage [3]. After years of long-term treatment often neither the patient nor its physician knows whether therapy is still based on pharmacological need, whether placebo dependency has developed, or that sheer habit is the reason for daily usage. High therapy satisfaction, rebound hyperacidity and previous therapy reduction failures make therapy cessation hard to accomplish in this group.
On-demand PPI treatment satisfies for the majority of GORD patients. Monotherapy results in mean daily consumptions of 0.3 up to 1 tablet a day [9, 10, 18, 19], whereas in combination with antacids needs of less than 0.5 PPI tablet were reported [20-24]. In all these studies first-time consulting patients were included, and on-demand treatment was initiated after a short period of standard treatment, which is the most ideal situation for titrating PPI needs.

Strengths and weaknesses of this study and in relation to other studies

Our study shows that a significant reduction in ASM consumption is accomplishable even after years of chronic use; patients were on ASM for a mean of 7 years. First, 19% virtually stopped treatment and 33% was satisfied on an on-demand regime of 2 - 6 tablets weekly (Table 2). Second, more than 50% of patients entering the study using 30 mg of a PPI or more experienced adequate relief on 20 mg daily or less (not shown). The calculated reduction in medication need of at least 28% is comparable with the results of above mentioned studies, despite various differences in study protocol. We included long-term users, employed monotherapy without antacids, and included patients needing more than a daily dosage in our calculation. The applicability of our findings is high in primary care, as the majority of patients with GORD symptoms on continuous acid suppression conforms to the selection criteria used in our study: uncomplicated GORD or stage A/B oesophagitis [25]. We conclude that a long history of acid suppressive treatment is no impediment for successful therapy reduction or termination.
A limitation of our study was the high drop-out during the run-in; 24% of patients could not be transferred to daily Pantoprazole 20 mg, raising the possibility of selection,

which limits generalizability. Of all patient- and disease-related characteristics only DDD of medication use prior to study entry differed between the randomized population and patients leaving during run-in, resulting in a selection towards patients with lower entrance dosages. However, we regard this selection of minor importance as the vast majority of patients dropping out used 20 mg of Omeprazole, indicating that the change in specific drug was the main reason for inadequate relief and not a dosage reduction.

Symptom control and quality of life are the most relevant issues in treatment of GORD. In mentioned on-demand studies, the patient's willingness to continue the study is used as an indirect measure for symptom control; the degree of symptom control, absolute and relative to standard treatment is not reported. If well-being was included, results of treatment failure were compared with treatment success [20, 21], or symptoms were compared between placebo and PPI on-demand treatment [22]. None of these studies correlated well-being or symptoms with the amount of acid suppression used. One non-randomized study showed that high quality of life at the end of short-term daily treatment was maintained during on-demand treatment [26].

We compared effectiveness of fixed daily PPI treatment with a self-adjusted dosage. At the final dosage, symptom control and quality of life were not significantly different between the two treatment groups (Figure 3), despite a difference of nearly 30% in the amount of medication used. However, in both groups a minority (8 and 24%) experienced a temporal decrease in symptom control and quality of life. Upon their complaints patients were advised to return to a daily dosage or more, and it was considered that at their final dosage symptom control and quality of life were soon restored to pre-adjustment levels. In the 76% of patients not experiencing difficulties in dosage adjustment, absolute disease-related- and general well-being were high and independent of the number of PPI tablets used (Table 3). The slight patient-specific decreases in three QolRad dimensions found in patients using less than 6 tablets weekly were however acceptable; these patients did not decide to use more medication or to discontinue the study for inadequate relief.

Implications for clinical practice

Our study once more confirms high placebo satisfaction of acid suppressive therapy. Of patients with adequate relief on placebo and using hardly any Pantoprazole, about 50% believed they were receiving daily Pantoprazole (Figure 2). Placebo satisfaction complicates translation of calculated pharmacological dependencies to daily practice; effective placebo treatment during a clinical trial with care and reassurance from a study nurse is not equivalent to termination of therapy in daily life. Yet, the 19%

terminating active treatment but on placebo in our study compares well with the 21% of GORD patients on long-term therapy discontinuing PPI treatment in a non-blinded study [27]. Temporal symptom recurrence, which was indeed seen in a minority of patients, furthermore complicates initiation and maintenance of on-demand and intermittent therapies. On the other hand, physicians have been shown to underestimate the willingness of patients to achieve the minimal effective dosage, and to actively participate in the treatment decision-making process [28]. Patients appear to accept temporal symptom recurrence in the knowledge that effective therapy is readily available. Furthermore, patients have been shown to worry about safety of PPI use [28], especially since adverse side-effects of long-term acid suppression appeared in public media; it could mask pre-existing malignancies [29], may increase the risk of infection with *Campylobacter* [30] and *Clostridium difficile* [31] and is associated with increased risks for pneumonia [32] and hip fracture [33].

In conclusion, a self-adjusted dosage minimizes drug usage without seriously impairing symptom control and quality of life. This treatment strategy should therefore replace daily therapy in patients with uncomplicated GORD. Proper information and support should help patients in adjusting the ASM dosage to their demands.

REFERENCES

1. Van Pinxteren B, Numans ME, Lau J, de Wit NJ, Hungin AP, Bonis PA. Short-term treatment of gastroesophageal reflux disease. *J Gen Intern Med* 2003;18:755-763.
2. 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.
3. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. *Postgrad Med J* 2007;83:66-68.
4. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008;336:2-3.
5. Richter JE, Bochenek W. Oral pantoprazole for erosive esophagitis: a placebo-controlled, randomized clinical trial. Pantoprazole US GERD Study Group. *Am J Gastroenterol* 2000;95:3071-3080.
6. Johnson DA, Benjamin SB, Vakil NB, Goldstein JL, Lamet M, Whipple J, *et al*. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. *Am J Gastroenterol* 2001;96:27-34.
7. Carlsson R, Galmiche JP, Dent J, Lundell L, Frison L. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. *Aliment Pharmacol Ther* 1997;11:473-482.

8. Fossmark R, Johnsen G, Johanessen E, Waldum HL. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. *Aliment Pharmacol Ther* 2005;21:149-154.
9. Bardhan KD. Intermittent and on-demand use of proton pump inhibitors in the management of symptomatic gastroesophageal reflux disease. *Am J Gastroenterol* 2003;98(Suppl 3):S40-48.
10. Lee TJ, Fennerty MB, Howden CW. Systematic review: Is there excessive use of proton pump inhibitors in gastro-oesophageal reflux disease? *Aliment Pharmacol Ther* 2004;20:1241-1251.
11. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Aliment Pharmacol Ther* 2007;26:195-204.
12. Pace F, Negrini C, Wiklund I, Rossi C, Savarino V. Quality of life in acute and maintenance treatment of non-erosive and mild erosive gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2005;22:349-356.
13. Prasad M, Rentz AM, Revicki DA. The impact of treatment for gastro-oesophageal reflux disease on health-related quality of life: a literature review. *Pharmacoeconomics* 2003;21:769-790.
14. Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol* 2001;96:1998-2004.
15. Ware JE, Kosinski M, Gandek B, Aaronson NK, Apolone G, Bech P, *et al*. The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol* 1998;51:1159-1165.
16. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, *et al*. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-1068.
17. Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey Manual and Interpretation Guide. Boston MA: New England Medical Center, The Health Institute; 1993.
18. Johnsson F, Moum B, Vilien M, Grove O, Simren M, Thoring M. On-demand treatment in patients with oesophagitis and reflux symptoms: comparison of lansoprazole and omeprazole. *Scand J Gastroenterol* 2002;37:642-647.
19. Juul-Hansen P, Rydning A. On-demand PPI requirements in patients with endoscopy-negative GERD. *J Clin Gastroenterol* 2004;38:746-749.
20. Bytzer P, Blum A, de Herdt D, Dubois D. Six-month trial of on-demand rabeprazole 10 mg maintains symptom relief in patients with non-erosive reflux disease. *Aliment Pharmacol Ther* 2004;20:181-188.

21. Lind T, Havelund T, Lundell L, Glise H, Lauritsen K, Pedersen SA, *et al*. On demand therapy with omeprazole for the long-term management of patients with heartburn without oesophagitis-a placebo-controlled randomized trial. *Aliment Pharmacol Ther* 1999;13:907-914.
22. Scholten T, Dekkers CP, Schutze K, Korner T, Bohuschke M, Gatz G. On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: the ORION trial. *Digestion* 2005;72:76-85.
23. Talley NJ, Lauritsen K, Tunturi-Hihnala H, Lind T, Moum B, Bang C, *et al*. Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: a controlled trial of 'on-demand' therapy for 6 months. *Aliment Pharmacol Ther* 2001;15:347-354.
24. Talley NJ, Venables TL, Green JR, Armstrong D, O'Kane KP, Giaffer M, *et al*. Esomeprazole 40 mg and 20 mg is efficacious in the long-term management of patients with endoscopy-negative gastro-oesophageal reflux disease: a placebo-controlled trial of on-demand therapy for 6 months. *Eur J Gastroenterol Hepatol* 2002;14:857-863.
25. Quartero AO, Numans ME, de Wit NJ. More abnormalities at upper endoscopy than expected by the General Practitioner. *Huisarts Wet* 2001;44:590-594.
26. Ponce J, Arguello L, Bastida G, Ponce M, Ortiz V, Garrigues V. On-demand therapy with rabeprazole in nonerosive and erosive gastroesophageal reflux disease in clinical practice: effectiveness, health-related quality of life, and patient satisfaction. *Dig Dis Sci* 2004;49:931-936.
27. Björnsson 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;24:945-954.
28. Grime J, Pollock K, Blenkinsopp A. Proton pump inhibitors: perspectives of patients and their GPs. *Br J Gen Pract* 2001;51:703-711.
29. Garcia Rodriguez LA, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. *Gut* 2006;55:1538-1544.
30. Neal KR, Scott HM, Slack RC, Logan RF. Omeprazole as a risk factor for campylobacter gastroenteritis: case-control study. *BMJ* 1996;312:414-415.
31. 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;294:2989-2995.
32. 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;292:1955-1960.
33. Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006;296:2947-2953.

5

Patient Selection for On-Demand PPI Therapy after Chronic Treatment of GORD: Trial and Error

ABSTRACT

Background

Transfer of GORD patients to an on-demand regime after years of continuous treatment proves difficult in daily clinical practice.

Aim

To identify patient characteristics in long-term continuous users of acid suppressive medication predicting eligibility for successful dosage reduction.

Methods

GORD patients who after long-term continuous treatment were able to reduce their dosage were compared to patients who persisted in a daily dosage with respect to general-, lifestyle-, quality of life characteristics (SF-36), psychological factors (SCL-90), symptom control on daily PPI (QolRad), disease- and medication history.

Results

Adequate symptom control on daily PPI and female gender were the only determinants independently associated with successful dosage reduction. The model including the QolRad vitality dimension and gender correctly predicted 64% of patients to both on-demand and sustained continuous treatment (area under ROC: 0.69).

Conclusion

No clinically useful combination of patient characteristics was able to adequately predict eligibility for successful dosage reduction in long-term treatment of GORD symptomatology. Successful transfer of patients to an on-demand regime remains a process of trial and error in which motivation of the patient and support by the physician will be important factors.

INTRODUCTION

The primary treatment goals for patients with gastro-oesophageal reflux disease (GORD) are relief of symptoms, healing of oesophageal lesions, and preventing relapses and complications [1, 2]. This is accomplished by treatment with acid suppressive medication (ASM), of which proton pump inhibitors (PPI) are most effective and most commonly used [3]. As GORD is considered to be a chronic disorder, initial short-term PPI treatment commonly evolves to long-term daily therapy. Since 1999, over 30 studies have been published on the so called 'on-demand' regime of PPI intake, focusing on medication savings, tolerability, patient satisfaction, relapse prevention and cost-effectiveness [4-6]. It appeared that on-demand therapy is an effective clinical strategy for the majority of GORD patients. Moreover, it is the most cost-effective approach. It has been estimated that 26 to 71% of patients presently on long-term daily PPI treatment could be switched to an on-demand regime [7].

Despite these conclusions and guidelines advocating non-continuous PPI therapy for GORD (Dyspepsia, NICE 2004) switching to on-demand PPI prescription has not yet integrated into routine clinical practice [8]; on-demand prescription accounts for just 27% [9, 10].

There are clear barriers for physicians to switch to on-demand treatment of patients who have been on continuous ASM for many years. In primary care many patients use chronic ASM for GORD symptoms without an evidence-based indication [11]. After many years of treatment neither the patient nor the physician is aware of the initial indication, and knows whether therapy is based on strict pharmacological need, on sheer habit, or whether placebo dependency has developed. High satisfaction with PPI therapy and previous reduction failures make it difficult to change PPI consumption in this group. We have recently shown that GORD patients on long-term ASM are very well able to reduce their medication intake without losing symptom control (*chapter 4*); 52% of chronic users reduced their dosage to less than 6 dosages per week.

In adhering to guidelines, it would be helpful to be able to identify patients eligible for a switch to on-demand therapy. In the present study we aim to identify patient characteristics and disease determinants predicting a successful switch by comparing patients who were able to reduce their dosage with those who persisted in a daily regime.

METHODS

Trial procedure: patient-controlled blinded dosage adjustment

The design and methodology of this study have been described previously (*chapter 4*). In short, primary care patients with a history of GORD on continuous ASM (defined as 180 defined daily dosages (DDD) or more per year) were eligible. Patients with a documented history of Barrett's oesophagus, oesophagitis C/D, with acute peptic ulcers, severe co-morbidity, and those using non-steroidal anti-inflammatory drugs were excluded.

Upon sustained symptom control after a 4 weeks run-in period on daily Pantoprazole 20 mg, patients were randomized to either daily placebo treatment with Pantoprazole as rescue medication, or to daily Pantoprazole with placebo rescue (double-blind, 13 weeks). Patients were instructed to use one capsule per day from the daily-container, and in case of symptoms one capsule daily from the rescue-container.

Measurements

At study entry information regarding gastrointestinal morbidity (registered by the general practitioner), years since first episode of GORD symptoms, ASM in use (type, DDD), *Helicobacter pylori* status (Pyloriset ELISA-G III, ORION), smoking (yes, no), alcohol use (never/rarely, <3, ≥3 consumptions/day), physical exercise (never/rarely, regularly, weekly) and the BMI (kg/m^2) was obtained. Patients were asked to complete the following questionnaires:

Quality of life in reflux and dyspepsia (QolRad)

The QolRad monitors disease-related quality of life in patients suffering from reflux; its outcome was shown to reflect treatment response and impact of symptoms [12]. It includes 25 items combined into 5 dimensions: emotional distress, sleep disturbance, vitality, food/drink problems and physical/social functioning. A 7-point scale is used to assess item severity or frequency (1: a great deal/all of the time, 2: a lot/most, 3: a moderate amount/quite a lot, 4: some, 5: a little, 6: hardly any, 7: none).

Symptom Check List 90 (SCL-90)

This validated questionnaire reflects psychological symptom state [13]. Using 90 items answered on a 5-point scale, it covers 8 dimensions of mental health: anxiety, phobic anxiety, depression, somatization, obsessive-compulsive behavior, interpersonal sensitivity, hostility and sleeping problems. A high score indicates the presence of a psychological symptom or psychiatric diagnosis.

SF-36 health survey

Using 36 questions generic quality of life is measured on 8 dimensions [14]: physical functioning, role limitations due to physical health problems, body pain, general health perception, vitality, social functioning, role limitations due to emotional problems and general mental health. Scores are converted to a 0-100 scale, with higher scores indicating higher levels of health or well-being.

Data analysis

We analyzed all 141 patients randomized to daily placebo with Pantoprazole rescue. Patients were classified as 1: those who needed 6 or more tablets per week (this group also comprised patients prematurely discontinuing the study for inadequate relief) or 2: those who used less than 6 tablets per week and are therefore eligible for on-demand therapy.

Statistical analyses were calculated using SPSS version 14.0. Groups were compared using the Students t- and χ^2-tests. Testing was two-tailed, with $p<0.05$ defined as significant. Multivariate logistic regression analysis was carried out using determinants with p-values less than 0.2. Backward-stepwise logistic modeling was performed with a cut-off value of 0.05 for expulsion from the model. The area under the receiver operating characteristic (ROC) curve was used to estimate the combined predictive value of determinants remaining in the final model. Calibration analysis was performed using the Hosmer-Lemeshow's goodness-of-fit test.

RESULTS

Background

In the original trial, 141 patients in the placebo arm blindly titrated their demand for PPI by using Pantoprazole escape. In follow-up 73 of them used less than 6 tablets per week (mean of 2.9) to reach symptom relief; they were considered as eligible for on-demand treatment. 34 patients used 6 to 7 tablets per week and they were, together with 34 patients who were unable to adjust their dosage towards symptom control, regarded as non-eligible. These two groups were compared with respect to the clinically relevant variables available (Table 1).

General-, lifestyle characteristics and generic quality of life: Age, gender, current smoking, consumption of alcohol and frequency of physical exercise did not differ between the two groups. Furthermore, neither BMI as a continuous variable nor categorized as normal-, overweight, and obesity varied between treatments. Generic

Table 1: Patient characteristics according to adopted treatment regime.

Patient characteristics		Reduction (n=73)	Daily (n=68)	p-value
General, lifestyle, quality of life				
Age		55 ± 11	57 ± 12	0.5
Gender (% male)		52	68	0.09
Smoking (% yes)		23	19	0.7
Alcohol (%)	never, rarely	34	50	0.13
	<3/day	56	45	
	≥3/day	10	5	
Phys exercise (%)	never, rarely	10	9	1
	regularly	7	7	
	weekly	83	84	
BMI		27.5 ± 4.4	27.2 ± 5.3	0.6
BMI (%)	<25	29	31	0.9
	25 - <30	51	50	
	≥30	20	19	
Physical SS		49.3 ± 9	48.6 ± 9.2	0.7
Mental SS		53.1 ± 8.3	54.2 ± 8.3	0.4
Psychological factors				
Anxiety		12.4 ± 2.6	13.6 ± 5.6	0.1
Phobic anxiety		7.9 ± 1.9	8.5 ± 3.7	0.2
Depression		20.6 ± 4.3	21.8 ± 7.8	0.3
Somatization		18.8 ± 4.7	19.4 ± 7.1	0.5
Obsessive-compulsive behavior		12.6 ± 3.3	13.9 ± 6.3	0.1
Interpersonal sensitivity		22.8 ± 5.9	24.4 ± 9.6	0.2
Hostility		7 ± 1.3	7.2 ± 1.9	0.3
Sleeping problems		5.4 ± 2.9	5.3 ± 2.7	1
Symptom control				
Emotional distress		6.8 ± 0.5	6.6 ± 0.7	0.04
Sleep disturbance		6.7 ± 0.5	6.2 ± 1.1	0.002
Food/drink problem		6.4 ± 0.8	6 ± 1	0.01
Phys/soc functioning		6.7 ± 0.6	6.5 ± 0.8	0.2
Vitality		6.5 ± 0.8	6 ± 1	0.003
Disease-, medication history				
Disease history (%)	hiatus hernia	6	8	0.7
	GORD, reflux, pyrosis	41	36	
	oesophagitis A	41	37	
	oesophagitis B	12	19	
Helicobacter pylori status (% positive)		25	22	0.8
Years 1st episode		7.6 ± 6.8	7.6 ± 4.8	1
DDD		325 ± 179	335 ± 136	0.7
DDD (%)	<360	57	46	0.3
	≥360	43	54	

Table 2: Logistic regression model with predictors of eligibility for dosage reduction.

Predictors	B (SE)	p-value	Exp(B)	95% CI Exp(B)
Gender (male=1)	- 0.85 (0.37)	0.023	0.43	0.2 - 0.9
QolRad vitality	0.62 (0.2)	0.002	1.85	1.3 - 2.7

Constant: -3.26

quality of life, by individual SF-36 values and summarized as physical and mental summary scores, did not differ between adopted regimes.

Psychological state: Patients in the two treatment groups did not differ significantly with respect to the scores on SCL-90 dimensions. Slightly higher values for anxiety and obsessive-compulsive behavior were found for patients demanding continuous treatment. After dichotomizing SCL-90 values (scoring above, or at and below the Dutch average value) no significant differences were found either (not shown).

Symptom control on daily PPI: After the run-in period on daily PPI patients were questioned about their residual reflux symptoms. Patients persisting in daily treatment expressed more hindrance of residual reflux symptoms during the run-in than patients reducing their dosage; high significance was found for sleep disturbance and vitality.

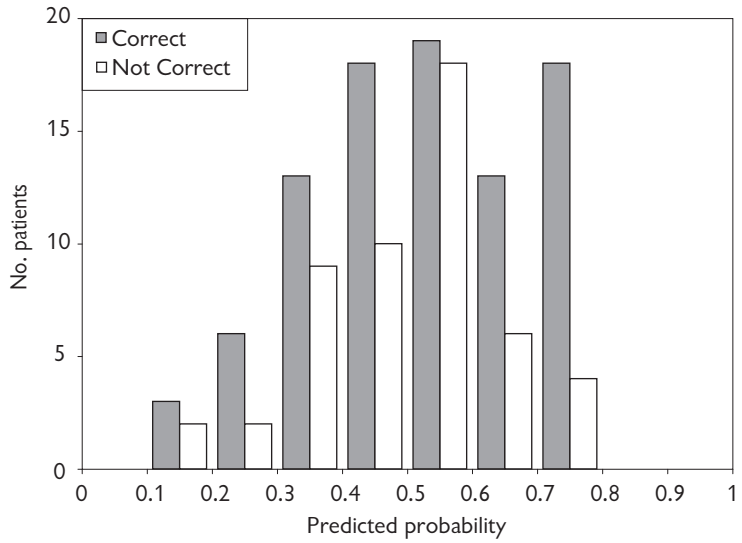


Figure 1: Plot of observed groups versus predicted probability.
The numbers of correctly and incorrectly predicted patients is plotted against the probability towards treatment regime; a value >0.5 (from the regression model) predicts dosage reduction and <0.5 daily treatment.

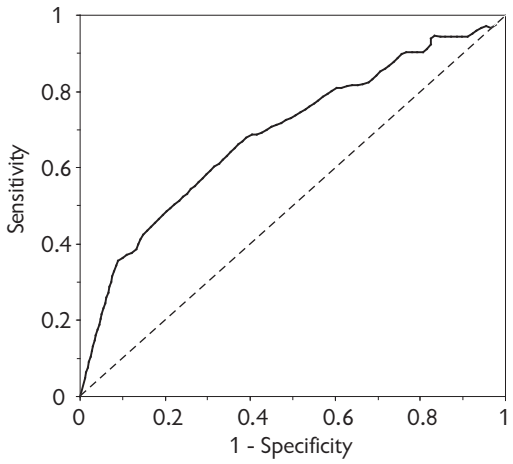


Figure 2: ROC curve belonging to the model containing QolRad vitality and gender.

Disease-, medication history: The indication for ASM treatment (hiatus hernia, GORD/reflux/pyrosis, oesophagitis), did not differ between the treatment regimes. When only patients with a history of oesophagitis were considered, no association was found for its grade. *Helicobacter pylori* status, years since first registered episode, nor DDD of ASM used prior to study entry (continuous and categorized) were associated with the treatment options reached.

When the joint impact of all variables obtained in this study was analyzed in logistic regression, the optimal model predicting the treatment regime included QolRad vitality and gender; a high score on QolRad vitality and female gender were indicative for dosage reduction (Table 2). This model correctly predicted 64% of patients to on-demand and 64% to sustained daily treatment (Figure 1). It was adequately calibrated across deciles of observed and expected risks (Hosmer-Lemeshow χ^2=3.6, p=0.7). The model discriminated marginally between patients eligible or not; the area under the ROC curve was 0.69, 95% CI: 0.6-0.77 (Figure 2).

DISCUSSION

With this study we aimed to find determinants predicting eligibility for successful dosage reduction after long-term continuous treatment of GORD by applying on-demand therapy. Of all variables tested, the presence of residual symptoms experienced while on daily PPI (via QolRad vitality) in combination with gender correctly predicted 64% of patients towards dosage reduction and towards sustained

daily treatment. Despite statistical significance and discriminative ability of this model, we do not consider this result of much clinical relevance for a number of reasons. First, without a prediction model 52 out of 100 patients in this defined population is able to reduce their dosage. The model predicts 55% of patients towards dosage reduction, of whom 64% is successful, resulting into 35 out of 100 patients reducing their dosage. We regard this loss large in comparison to the savings in time investment by the physician. Second, residual symptoms while on daily PPI will already be one of the main predictors in consideration; physicians are not likely to suggest medication reduction to patients communicating residual symptoms. Third, the QolRad vitality dimension is difficult in obtaining verbal information from the patient. When QolRad vitality in the model was replaced by 'sleep disturbance' or 'food/drink problems', which are easier to question, correct prediction of dosage reduction decreased to 57%.

In this study we did not find additional patient- or disease characteristics that might help the physician to identify patients for a successful transfer to on-demand therapy. We discuss potential determinants of dosage reduction found in literature.

First, erosive oesophagitis was shown to predict failure of dosage reduction, and was strongly associated with continuous medication intake [15, 10]. About half of our patients had mild oesophagitis at least one year ago, which did not influence dosage reduction success. We conclude that after one year successful PPI treatment mild oesophageal lesions are healed, and that their history does not influence the ability of patients to reduce their dosage.

Second, a higher BMI was shown to increase the need for PPI medication, with an association between number of pills and weight of 2.3/month/BMI-group [16]. Recent weight gain had more impressive results on medication necessity, but was not considered in our study. A possible explanation that BMI did not appear as a predictor is that we did not analyze the exact number of pills in a population needing mediation, but dichotomized into needing daily treatment and less than daily treatment.

Finally, the original clinical indication for ASM use and other disease-related determinants -a clear description of initial symptoms, interim evaluations, endoscopy, pH monitoring- might contribute to predict successful dosage reduction. Due to the primary care origin, this kind of information was not available in our study.

Might patient selection have contributed to the absence of more predictors? Three selection steps were made during the study. The general practitioner screened for patients with uncomplicated GORD, eligible for a study on dosage defining (not explicitly dosage reduction). Patients decided to participate or not, and finally they had to pass a 4 weeks run-in on daily Pantoprazole. As patients dropping out during

run-in did not differ from those entering the randomized phase with respect to the variables described here (results not shown), selection bias is unlikely at this step. Furthermore, selection by the physician and patients' decision to participate will resemble decisions made in daily practice. We therefore regard our study population representative for the large group of GORD patients that may be considered for dosage reduction.

Still this group of patients is heterogeneous with respect to symptomatology, treatment response, placebo dependency, lifestyle and psychological well-being. All these factors probably influence the required treatment regime, and due to their multitude and diverse nature it proves difficult to identify a strong set of determinants predicting the optimal treatment regime. We conclude that a successful transfer from daily to less than daily treatment remains a matter of trial and error. In this process motivation of the patient and the physician will be important factors for success.

REFERENCES

1. Bytzer P, Blum AL. Personal view: rationale and proposed algorithms for symptom-based proton pump inhibitor therapy for gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2004;20:389-398.
2. Heidelbaugh JJ, Nostrant TT, Kim C, van Harrison R. Management of gastroesophageal reflux disease. *Am Fam Physician* 2003;68:1311-1318.
3. 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.
4. Metz DC, Inadomi JM, Howden CW, van Zanten SJ, Bytzer P. On-demand therapy for gastroesophageal reflux disease. *Am J Gastroenterol* 2007;102:642-653.
5. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Aliment Pharmacol Ther* 2007;26:195-204.
6. Gerson LB, Robbins AS, Garber A, Hornberger J, Triadafilopoulos G. A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. *Am J Gastroenterol* 2000;95:395-407.
7. Lee TJ, Fennerty MB, Howden CW. Systematic review: Is there excessive use of proton pump inhibitors in gastro-oesophageal reflux disease? *Aliment Pharmacol Ther* 2004;20:1241-1251.
8. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008;336:2-3.
9. Meineche-Schmidt V, Hvenegaard A, Juhl HH. Participation in a clinical trial influences the future management of patients with gastro-oesophageal reflux disease in general practice. *Aliment Pharmacol Ther* 2006;24:1117-1125.

10. Nocon M, Labenz J, Jaspersen D, Meyer-Sabellek W, Stolte M, Lind T, Malfertheiner P, Willich SN. Long-term treatment of patients with gastro-oesophageal reflux disease in routine care -results from the ProGERD study. *Aliment Pharmacol Ther* 2007;25:715-722.
11. Batuwitage BT, Kingham JG, Morgan NE, Bartlett RL. Inappropriate prescribing of proton pump inhibitors in primary care. *Postgrad Med J* 2007;83:66-68.
12. Talley NJ, Fullerton S, Junghard O, Wiklund I. Quality of life in patients with endoscopy-negative heartburn: reliability and sensitivity of disease-specific instruments. *Am J Gastroenterol* 2001;96:1998-2004.
13. Derogatis LR, Rickels K, Rock AF. The SCL-90 and the MMPI: a step in the validation of a new self-report scale. *Br J Psychiatry* 1976;128:280-289.
14. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055-1068.
15. Cote GA, Ferreira MR, Rozenberg-Ben-Dror K, Howden CW. Programme of stepping down from twice daily proton pump inhibitor therapy for symptomatic gastro-oesophageal reflux disease associated with a formulary change at a VA medical center. *Aliment Pharmacol Ther* 2007;25:709-714.
16. Sheu BS, Cheng HC, Chang WL, Chen WY, Kao AW. The impact of body mass index on the application of on-demand therapy for Los Angeles grades A and B reflux esophagitis. *Am J Gastroenterol* 2007;102:2387-2394.

6

Supporting Differential Diagnosis of GORD with Weighed Patient Characteristics in Primary Care

ABSTRACT

Background

For a differential diagnosis of gastro-oesophageal reflux disease (GORD), which is important in choosing the optimal treatment strategy, general practitioners depend on history, symptom assessment and upper gastrointestinal endoscopy (UGE).

Aim

We explored the possibilities of a prediction rule based on symptoms and history to distinguish patients with non-erosive GORD, mild, and severe erosive GORD.

Methods

A prediction rule was validated in a new population of patients referred for UGE. Cut-off points for the risk-score were evaluated with respect to non-erosive disease, oesophagitis grade A to D and Barrett's.

Results

In the new population the rule showed discriminative ability on oesophagitis/Barrett's with an AUC of 0.66. Two clinically relevant cut-off points were defined resulting in groups of patients needing re-evaluation (non-erosive), needing empirical proton pump inhibitor treatment (grade A/B), and requiring continuous treatment and UGE (grade C/D/Barrett's).

Conclusion

The prediction rule proved to be useful as additional support in decisions like treatment options and referral strategy for GORD patients in primary care.

INTRODUCTION

Differential diagnosis of upper gastrointestinal symptomatology, with an incidence of 3 to 4% of all consultations, is a common problem in primary care [1]. No gold standard is available to diagnose gastro-oesophageal reflux disease (GORD) or functional dyspepsia. Current guidelines advise general practitioners (GP) to use a symptom-based, patient-centered approach of structured interview [2, 3], if necessary in combination with the proton pump inhibitor (PPI) test to diagnose GORD [4]. According to this Montreal consensus additional diagnostic testing with upper gastrointestinal endoscopy (UGE) is postponed and only recommended for those with alarm features, symptoms longer than five years, or symptoms unresolved by standard therapy [5, 6]. However, it remains difficult to distinguish patients with functional dyspepsia, benign GORD, and more severe conditions like erosive oesophagitis and Barrett's oesophagus. The cardinal GORD symptoms, heartburn and acid regurgitation, lack specificity [7, 8], and no difference in symptom severity is detected between patients with erosive and non-erosive disease [9, 10].

A confirmed diagnosis with UGE early at onset of disease determines its short-term management, could justify long-term treatment with acid suppressive medication (ASM), and would provide a solid basis for physicians and patients to discuss treatment options during the future course of disease. Therefore, 'prompt endoscopy' for evaluation of dyspepsia seemed very attractive in the nineties [11].

PPI treatment is the preferred therapy for GORD, long-term continuously for patients with severe oesophageal erosions (grade C/D) or on-demand with possibly (temporal) cessation of therapy for patients with mild erosions (grade A/B) [12]. To make such a management decision GPs rely on patients' history, symptom assessment, response to PPI treatment, and sometimes make use of UGE. A prediction rule to distinguish patients with benign GORD without severe erosions, for whom neither UGE nor long-term treatment is indicated, would be useful.

In this study we explore the possibilities of a prediction rule based on symptom evaluation and history to distinguish patients needing long-term treatment or UGE to check on severe oesophagitis or (pre)-malignant disease, from those who can be stepped down after an empirical PPI trial, and those who do not need PPI treatment but re-evaluation instead.

METHODS

The prediction rule

The prediction rule (outcome: oesophagitis) was developed by transformation of a multiple logistic regression model derived from a population of 861 patients referred by their GP for UGE for the first time [13, 14]. It comprises 8 characteristics: gender, history of hiatus hernia, heartburn at night, smoking of >15 cigarettes/day, symptoms at bending over, pain on empty stomach, history of peptic ulcer, and use of ASM. To provide an easily manageable score list, the regression coefficients of the optimal regression model were divided by 0.28, which was the coefficient for use of ASM, and rounded to the nearest integer (Table 1). With this score list a risk-score can be calculated for any individual patient for whom the GP considers an empirical PPI trial or UGE referral.

Test population

The prediction rule was validated using data of 1138 primary care patients, also referred for their first UGE by 150 GPs from the same region, yet in a following period. Information on patient and disease characteristics was obtained from the application form filled in by the GP at referral. UGEs were performed in 9 hospitals by 22 endoscopists whom all received instructions to obtain an acceptable degree of comparability in the report of their findings. Anonymized copies of application forms and endoscopy reports were sent to the researchers to be evaluated. The procedure was approved by the Ethics Committee of the University Medical Center Utrecht.

Table 1. Score system based on a prediction model for oesophagitis.

Characteristic	OR original	95% CI	OR test	95% CI	score
Gender (male)	2.2	1.3 - 3.5	1.4	1.1 - 1.9	+3
History hiatus hernia	2.7	1.5 - 4.6	3.1	2.1 - 4.6	+3
Heartburn at night	1.8	1.1 - 3	1.5	1.1 - 2	+2
Smoking >15/day	1.6	0.9 - 2.8	1	0.7 - 1.5	+2
Symptoms at bending over	2	1.2 - 3.2	2.4	1.8 - 3.2	+2
Pain on empty stomach	0.4	0.2 - 0.6	0.7	0.5 - 0.9	-4
History of peptic ulcer	0.3	0.1 - 0.6	0.5	0.3 - 0.8	-4
Use of ASM	0.8	0.5 - 1.2	0.9	0.7 - 1.2	-1

Maximal score: 12, minimal score: -9, OR: odds ratio, CI: confidence interval.

Data analysis

As the prediction rule was designed for selection of oesophagitis upon UGE, the outcome was defined as oesophagitis grade A-D, with Barrett's as a distinct group. All other endoscopic findings were classified as non-oesophagitis. By using the prediction rule, a risk-score for the presence of oesophagitis/Barrett's was calculated for each patient in the test population. In the range of possible risk-scores, several cut-off points were chosen to find appropriate risk-scores at which one might consider to start PPI therapy, or refer for UGE. Considering the score as a diagnostic test for the presence or absence of oesophagitis/Barrett's, at each cut-off point sensitivity, specificity and positive and negative predictive values were calculated by using 2x2 tables (expected versus observed patients with or without oesophagitis/Barrett's). The optimism of the model was determined by comparing the area under the ROC curves obtained from the original population and from the test population.

RESULTS

For evaluation of the prediction rule data from 1107 patients of the test population could be used; 7 were excluded because of indications beyond the scope of this study and 24 UGEs were unsuccessful. The prevalence of oesophagitis in this test population was similar as in the original population, respectively 22.9 and 20%. Malignancies, ulcers (duodenal and gastric) and other relevant findings like oesophagusvarices, achalasia and polyps were found in 1.4, 12 and 4% of patients respectively. The prevalence of minor findings (hiatus hernia without oesophagitis, low-grade gastritis/duodenitis) was 28.8%. Normal UGE results (including healed ulcers and scars) were found in 30.9% of patients.

Individual risk-scores were calculated using the prediction rule (Table 1); male gender, known history of hiatus hernia, heartburn at night, smoking of more than 15 cigarettes a day and symptoms at bending over predisposed to oesophagitis, pain on

Table 2. The score system as a diagnostic test for erosive GORD.

Cut-off point	Sensitivity	Specificity	+PV	-PV	% n ≤cut-off point
-3	93.4	16.3	24.9	89.7	14
-2	90.5	22.8	25.8	89	19.8
-1	84.2	32.6	27	87.4	28.7
0	75.5	47.2	29.8	86.7	42
+1	65.6	52.7	29.1	83.9	48.5

PV: predictive value, n=1107.

Table 3. Distribution of patients with different grades of oesophagitis over risk-groups.

	-9 to -3	-2 to +1	+2 to +12	Total
Barrett's	0	11	29	40
Oesophagitis D	0	0	5	5
Oesophagitis C	0	3	7	10
Oesophagitis B	2	7	21	30
Oesophagitis A	14	50	104	168
Total	16	71	166	253

empty stomach, history of peptic ulcer and use of ASM 'protected'. In the test population the prediction rule showed an AUC of 0.66 (95% CI: 0.62-0.7), compared to 0.77 (95% CI: 0.71-0.82) for prediction of oesophagitis in the original population.

For the rule being used as a management decision instrument, two cut-off points for the risk-scores were derived from the data. A score higher than -3 is proposed for initiating empirical PPI treatment. At -3, sensitivity and specificity were 93.4 and 16.3%, whereas positive and negative predictive values were 24.9 and 89.7% (Table 2). No oesophagitis C/D or Barrett's was found in the 14% of patients scoring -3 and lower (Table 3). With scores from -2 up to +1, patients were beginning to show relevant erosions; all patients needing PPIs would have received this treatment when the rule was being used.
A score higher than +1 is proposed for UGE referral (sensitivity and specificity: 65.6 and 52.7%, and positive and negative predictive values: 29.1 and 83.9%); all oesophagitis grade D was in this high risk-group (Table 3). When the rule would have been used, 48.5% of patients of this population would not have been referred for UGE at the expense of missing 27.5% of Barrett's cases and 30% of patients with oesophagitis C.

DISCUSSION

The performance of a prediction model to distinguish patients not needing PPI treatment, from those requiring empirical PPI treatment, or prompt UGE was validated in a population of patients referred by their GP for UGE. In the validation population the prediction rule lost discriminative ability (AUC of 0.66 versus 0.77 in the original population). A poorer performance of a model in the validation population is usually found in diagnostic research [15, 16]. Additional explanations might be the

simplification of the original model into a practical prediction rule, changes in referral attitude of GPs due to the introduction of new dyspepsia guidelines [4], the availability of new drugs for dyspepsia management, and by a change in epidemiological distribution of disease during the follow-up period [5].
It could be argued that prediction with an AUC of 0.66 has a limited role in diagnosis. However, despite its marginal discriminative ability, we will discuss the applicability of the rule as additional support in the treatment decisions the GP makes for patients suspected of GORD.

We found that the prediction rule was able to discriminate oesophagitis from non-oesophagitis given the AUC of 0.66, which is an interesting finding. First, this rule discriminated similarly as other prediction rules or questionnaires for GORD [16, 17]. Since confirmed oesophagitis was our outcome, one might expect that contrast would have been reduced by non-erosive GORD in the reference group. Second, many experts consider 'organic manifestations of GORD' indistinguishable from 'endoscopy-negative GORD' by means of patients' history [6, 9, 10, 18]. When this would be true, our rule would not have been able to discriminate oesophagitis from endoscopy-negative GORD, which it showed to do (Table 3). Therefore, there might be a subtle gradual difference in symptomatology between non-erosive and erosive GORD. This was suggested earlier as PPIs were shown to have a more pronounced advantage over histamine-2-receptor antagonists (H2RA) in treatment of uninvestigated GORD (by definition including erosive GORD), than in confirmed non-erosive GORD [12].

Currently, GORD is being diagnosed primarily by a combination of disease history and symptom assessment [2, 3, 6], and no non-invasive tools are available for predicting the presence and severity of oesophageal lesions [18]. This remains a problem in primary care as the grade of oesophagitis at least partially determines the most appropriate treatment: symptomatic treatment with antacids or H2RAs for non-erosive disease, a 4 to 8 weeks trial of PPIs for grade A/B, and long-term continuous PPI treatment for grade C/D and Barrett's. Oesophagitis tends to be under-diagnosed by GPs [19], while grade C/D are evidence-based indications for long-term PPI treatment. On the other hand, patients with grade A/B benefit from an empirical PPI trial for symptom relief and healing lesions, but are not indicated for chronic PPI treatment and need to be stepped down in case of adequate relief. In these respects, the aim is not only to diagnose GORD or oesophagitis, but being able to distinguish non-erosive from mild-, and mild- from severe erosive GORD. With this aim the negative predictive values at the cut-off points of -3 and +1 are acceptable.

What will be the benefits and possible risks of using the prediction rule? Not initiating PPI treatment with patients scoring -3 or lower does not harbour a great risk, as the few patients with oesophagitis A/B in this group have a large chance of becoming treated with H2RAs, which are effective for these lesions. Furthermore, functional dyspepsia and testing for *Helicobacter pylori* can be considered for this low risk-group (14%). The benefit of not initiating PPI therapy in this group of patients is that it will prevent patients from becoming unnecessary, maybe placebo-dependent, chronic PPI users.
When PPI therapy is initiated at a risk-score of -2 and higher, all patients with oesophagitis C/D and Barrett's will receive PPI treatment. The risk however of tapering down PPI use upon symptom relief for patients scoring below +2 is that 27.5% of Barrett's patients and 30% of patients with oesophagitis C will temporarily be deprived of PPIs, as their evidence-based indication for continuous treatment (by UGE) will be missed. Probably during follow-up these patients will end up for UGE anyway, because of therapy failure, frequent relapses or age.
Using +2 and higher for UGE referral, all patients with oesophagitis D and the vast majority of Barrett's and grade C would have been referred. This is desirable as these indications justify long-term continuous PPI treatment, and furthermore, patients with Barrett's need to be investigated regularly to be able to intervene when high-grade dysplasia occurs [20]. At this cut-off point a theoretical reduction of 50% in referrals could be obtained. This reduction is at the expense of missing patients with oesophagitis C and Barrett's. However, when patients with alarm symptoms are referred anyway, less patients with oesophagitis C and Barrett's will be missed [14].

Concluding, the prediction rule described in this study can be supportive for the GP in treatment decisions for patient suspected of GORD. A theoretical reduction of 48.5% of UGE referrals for diagnosing GORD can be obtained, non-indicated chronic use of ASM can be prevented, while the vast majority of patients do receive adequate treatment. Adjusting the model with additional patient characteristics to further optimize differential diagnosis of GORD, and its implementation will remain of interest for the future.

REFERENCES

1. Van der Linden MW, Westert GP, de Bakker DH, Schellevis FG. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Klachten en aandoeningen in de bevolking en in de huisartspraktijk. NIVEL/RIVM, 2004.
2. Fass R. Symptom assessment tools for gastroesophageal reflux disease (GERD) treatment. *J Clin Gastroenterol* 2007;41:437-444.

3. Flook N, Jones R, Vakil N. Approach to gastroesophageal reflux disease in primary care: Putting the Montreal definition into practice. *Can Fam Physician* 2008;54:701-705.
4. De Wit NJ, van Barneveld TA, Festen HP, Loffeld RJ, van Pinxteren B, Numans ME. CBO-NHG richtlijn maagklachten. *Ned Tijdschr Geneeskd* 2005;149:1386-1392.
5. Van Kerkhoven LA, van Rijswijck SJ, van Rossum LG, Laheij RJ, *et al*. Open-access upper gastrointestinal endoscopy a decade after the introduction of proton pump inhibitors and *Helicobacter pylori* eradication: a shift in endoscopic findings. *Digestion* 2007;75:227-231.
6. 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;101:1900-1920.
7. Klauser AG, Schindlebeck NE, Müller-Lissner SA. Symptoms in gastro-oesophageal reflux disease. *Lancet* 1990;335:205-208.
8. Lewin van den Broek NT, Numans ME, Buskens E, Verheij TJ, de Wit NJ, Smout AJ. A randomised controlled trial of four management strategies for dyspepsia: relationships between symptom subgroups and strategy outcome. *Br J Gen Pract* 2001;51:619-624.
9. Chen CL, Orr WC, Yang CC, Kuo TB. Cardiac autonomic regulation differentiates reflux disease with and without erosive oesophagitis. *Scand J Gastroenterol* 2006;41:1001-1006.
10. El-Serag HB, Johanson JF. Risk factors for the severity of erosive esophagitis in *Helicobacter pylori*-negative patients with gastroesophageal reflux disease. *Scand J Gastroenterol* 2002;37:899-904.
11. Bytzer P, Moller Hansen J, Schaffalitzky de Muckadell OB. Empirical H2-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* 1994;343:811-816.
12. Van Pinxteren B, Numans ME, Lau J, de Wit NJ, Hungin AP, Bonis PA. Short-term treatment of gastroesophageal reflux disease. *J Gen Int Med* 2003;18:755-763.
13. Numans ME, van der Graaf Y, de Wit NJ, Touw-Otten FW, de Melker RA. How much ulcer is ulcer-like? Diagnostic determinants of peptic ulcer in open access gastroscopy. *Fam Prac* 1994;11:382-388.
14. Numans ME, van der Graaf Y, de Wit NJ, de Melker RA. How useful is selection based on alarm symptoms in requesting gastroscopy? *Scand J Gastroenterol* 2001;36:436-443.
15. Carlsson R, Dent J, Bolling-Sternevald E, Johnsson F. The usefulness of a structured questionnaire in the assessment of symptomatic gastroesophageal reflux disease. *Scand J Gastroenterol* 1998;33:1023-1029.
16. Numans ME, de Wit NJ. How can reflux symptoms be recognized in primary care? a diagnostic evaluation of the Carlsson-Dent GERD questionnaire. *Aliment Pharmacol Ther* 2003;17:1049-1055.
17. Aanen MC, Numans ME, Weusten BL, Smout AJ. Diagnostic value of the reflux disease questionnaire in general practice. *Digestion* 2006;74:162-168.

18. Moayyedi P, Talley NJ. Gastro-oesophageal reflux disease. *Lancet* 2006;367:2086-2100.
19. Quartero AO, Numans ME, de Wit NJ. More abnormalities at upper endoscopy than expected by the General Practitioner. *Huisarts Wet* 2001;44:590-594.
20. Das D, Ishaq S, Harrison R, Kosuri K, *et al*. Management of Barrett's esophagus in the UK: overtreated and underbiopsied but improved by the introduction of a national randomized trial. *Am J Gastroenterol* 2008;103:1079-1089.

7

General Discussion

BACKGROUND

In this thesis we describe the results of the ELISE study. The primary aim of this study was to characterize patients with gastro-oesophageal reflux disease (GORD) who are pharmacologically dependent on long-term continuous acid suppressive medication (ASM). The seemingly opposite secondary aim, and the particular interest of many participating general practitioners was to determine whether and which GORD patients on long-term ASM can terminate or reduce this treatment. Although from different perspectives, both aims are compatible and relevant.

Primary care deals with a large group of long-term continuous users of ASM for GORD symptomatology without evidence-based indication for their use. After years of treatment neither the patient nor the general practitioner knows whether there truly remains daily pharmacological need. Non-continuous therapies -on-demand or intermittent- or even termination of therapy have been advocated for these patients by guidelines and insurance companies to prevent unnecessary medication use, adverse side-effects of long-term acid suppression, medicalization, and for budgetary reasons. Nevertheless, high therapy satisfaction, failures in dosage reduction, and dissatisfied patients are barriers for general practitioners to switch to a different treatment regime in patients who have been on continuous ASM for many years. To stimulate this change more evidence is needed about the magnitude of unnecessary ASM use in this group, and how patient-controlled dosage reduction affects treatment satisfaction. Additionally, fine-tuning marketing strategies for ASM, and accentuating guidelines towards definitions for long-term continuous use, would also aid in reducing prescription.

CURRENT KNOWLEDGE

- despite evidence for overuse of ASM for GORD, transfer to on-demand- or cessation of acid suppressive therapy proves difficult in daily clinical practice
- no published data describe the impact of dosage reduction on well-being after longstanding acid suppression

ELISE STUDY

Study design

The ELISE study was designed as a randomized, double-blind, 'fixed regime rescue' trial with patients invited by their general practitioner for dosage adjustment. After run-

in on daily Pantoprazole patients were randomized to either daily placebo with Pantoprazole rescue, or to daily Pantoprazole with placebo rescue. Why the complexity of this design?

We aimed to investigate strict pharmacological dependency with minimal interference by placebo effects. Patients on daily placebo were blindly titrating their pharmacological need for Pantoprazole by anticipating on perceived symptoms, and learning how to treat them: with a daily dosage, one dosage every two days, just in the weekends, or with short intervals. As they had a daily regime with placebo, minimal effects by placebo dependency were expected. The other arm was needed to blind the study, and served as a valid control for patients' satisfaction.

WHAT THIS STUDY ADDS

- a significant placebo response is apparent in chronic users of ASM and pharmacological dependency is overestimated
- more than 50% of GORD patients can be switched from daily to on-demand treatment without impairing symptom control and quality of life
- during adjustment, a minority of patients experiences a (temporal) decrease in well-being

Results on dosage reduction

The data presented in *chapter 4* proved a clear message to general practitioners. At least 52% of chronic ASM users for GORD symptomatology is able to significantly reduce their dosage while maintaining symptom control and quality of life. 24% of patients continues their daily dosage with no effect on well-being, whereas 24% experiences a decline in symptom control and quality of life during the adjustment phase. These patients probably need an additional contact with the general practitioner to discuss the best treatment option; in the study they were classified as needing one daily dosage or more.

Disadvantages of the study design

Several protocol-related problems were encountered that need discussion. First, the study had a high drop-out. Due to inadequate relief on daily Pantoprazole 24% of patients discontinued the study during run-in, raising the possibility of selection which may limit the generalizability. Of all patient- and disease-related characteristics only the DDD of medication use prior to study entry differed between the randomized

population and patients leaving during run-in, resulting in a selection towards patients with lower entrance dosages. However, we regard this selection of minor importance as the vast majority of patients dropping out used 20 mg or less of another PPI, Omeprazole, indicating that the change in specific drug was the main reason for inadequate relief and not a dosage reduction. Furthermore, 24% of patients in the daily placebo arm was unable to adjust their PPI dosage towards symptom control, and also discontinued the study. This was unexpectedly high as these patients adequately controlled their symptoms during the run-in on daily Pantoprazole, and also had the opportunity of a daily dosage in the randomized phase. For some of them the study protocol or aim was not clear, given reactions like: "my doctor gave me one tablet and I don't want to take two" or "you see, I can't reduce my dosage, I quit the experiment"! As these patients were classified as needing a daily dosage or more, pharmacological need may have been overestimated.

Second, to validly determine strict pharmacological dependency the blindness of the study is important. As the majority of patients unasked expressed their idea about the randomization arm they thought they were participating in, an impression about the actual blindness was obtained. Of patients in the daily placebo arm adjusting to two dosages or more per week as much as 96% indeed judged receiving daily placebo. Probably due to rebound hypersecretion of gastric acid upon cessation of PPI intake at entering the randomized phase, patients felt they were deprived of active medication. Instead of overcoming this period and subsequently titrating their actual need, patients could also have taken what they thought they needed. Again two commonly heard reactions: "I have had an inflammation of my oesophagus, I really need medication", or "I'm missing the valve between stomach and oesophagus, I depend on my pills"! As it is not clear whether all patients really tried to adjust their dosage, again pharmacological need might be overestimated. Initially, the study was designed to measure strict pharmacological dependency, but shifted by the lack of real blindness -for at least a subgroup of patients- towards dependency on medication.

Third, absence of pharmacological need was demonstrated in the 20% of patients adjusting to less than two dosages per week. Interestingly, half of them thought they were receiving daily Pantoprazole; these patients can be regarded as highly placebo-dependent. Although they showed to be independent of acid suppression, it is unclear whether they can terminate treatment in daily life. Effective placebo treatment in a supervised trial is not equivalent to termination of therapy in daily life. Because of placebo dependency, the calculated percentage of patients able to reduce their medication could be overestimated.

There are a number of ways to prevent the above mentioned protocol-related problems. The study could have been performed with the medication the patients used at entry to prevent drop-out by a brand switch. With the aim to determine how many and which patients can reduce their ASM, an open trial, in which patients reduce their medication in predetermined steps until an amount where symptoms start interfering, probably most easily translates into clinical practice. From a scientific and medical point of view, determinants of strict pharmacological dependency on long-term acid suppression remain of interest, especially for future management of GORD. In designing the perfect trial more attention needs to be paid to blind the study by masking or preventing rebound hypersecretion. This could be accomplished by providing high dosages of antacids after the transition, or by introducing various blinded reduction schemes, for example two weeks on half a daily dosage, next two weeks this dosage every two days, prior to the actual dosage adjustment phase. Initial stages could also be supported by antacids.

Prediction of patients eligible for successful dosage reduction

Differences between patients sustaining their daily dosage and patients able to reduce their dosage would be helpful in the decision process to identify patients eligible for on-demand treatment. Intuitively, from literature and own data (*chapters 2 and 3*) we expected to find predictors like prior oesophagitis, ASM dosage used at study entry, BMI, *Helicobacter pylori* status and psychological factors. As outlined in *chapter 5* no clinically useful combination of characteristics was found to predict successful dosage reduction.

There are three likely reasons for the absence of strong predictors. First, as outlined earlier, pharmacological- as well as placebo dependency, and also motivation and physiology to overcome rebound hypersecretion intervene in the dosage adjustment process. These mechanisms will each have their own set of predictors. These might be initial treatment indication, symptomatology, treatment response, *H. pylori* status and lifestyle for pharmacological need, and psychological factors, time on ASM, quality of life and disease perception for placebo need and motivation. Given these different mechanisms, it is difficult to filter out an overriding set of determinants in the small groups of patients we had in the study.
Second, for clinical applicability a dichotomy was created at needing a daily dosage or more versus the rest. Patients adjusting to one dosage every other day can however still be pharmacologically dependent on acid suppression, which may have reduced contrast. Analyses were also performed to distinguish patients needing medication or not (less than two weekly dosages versus the rest) and on the number of dosages

needed in linear regression. Still, no significant predictors were identified.
Third, no detailed or updated information was available on disease characteristics at the beginning of treatment nor from follow-up, like a description of the nature, severity and frequency of initial symptoms, treatment response, evaluations of previous dosage adjustments, recent endoscopy or pH monitoring. These items could be relevant in eligibility for dosage reduction.

MANAGEMENT STRATEGIES TO REDUCE ASM USE FOR GORD SYMPTOMATOLOGY

As selection of patients for successful dosage reduction proves difficult, which strategies could be used in primary care to reduce the number of long-term continuous users of ASM?
First, a minimal intervention strategy could be a good option as it includes the selection steps used in our study. This selection was straightforward: chronic users of ASM were selected via the local pharmacy and were subsequently screened by the general practitioner for a history of GORD symptomatology and for the absence of an evidence-based indication for long-term continuous use. The general practitioner can contact these patients via a letter advising them to switch to an on-demand regime: "only take your medication when you experience symptoms". Patients responding to this request are likely to be similar to the patients willing to participate in our trial. The letter should explain that selected patients do not have a medical indication for prolonged use, that oesophagitis in the past or a hiatus hernia do not impede successful dosage reduction, and that unnecessary long-term use could have adverse side-effects. Attention should be paid to explaining the effects of temporal rebound hypersecretion of gastric acid; a transition period of alternate day treatment or support by antacids can be advised. Patients can be offered a consultation if they have questions, or experience difficulties during dosage adjustment. Follow-up contacts

IMPLEMENTATION

- predicting eligibility for on-demand treatment appears difficult
- minimal intervention strategy
  → letter to patients
- postponing (chronic) ASM use
  → differential diagnosis of GORD
  → non-continuous therapy directly after 4-8 weeks empirical treatment
  → self-medication with OTC PPIs

can be included to increase the response; when patients phone for a repeat prescription they can be invited for a consultation to evaluate their experiences or to further motivate them. A similar minimal intervention strategy aimed at reducing and discontinuing benzodiazepine use in long-term users was shown to be successful; 27% of patients receiving the letter terminated benzodiazepine use, and consumption decreased by 20% in the group unable to terminate completely [1, 2]. Given the effect of minimal intervention strategies, the straightforward patient selection, and the minimal time investment by the general practitioner, it is worth trying a similar strategy for long-term users of ASM.

Second, in addition to reducing the number of long-term users by stimulating dosage reduction and reducing prescription, it makes sense to prevent patients from becoming a long-term user. This goal is complicated by the fact that there is no gold standard for an objective diagnosis for GORD; clinical history taking, as well as the PPI test showed low specificities. As a result, the vast majority of patients suspected of GORD will currently be treated empirically, which can end up in long-term PPI treatment of patients for whom a proper diagnosis was never made. Moreover, diagnosing GORD in primary care is difficult, but getting an impression about the presence and severity of erosions or complications is even more difficult. As these differential diagnoses determine the optimal treatment strategy, for many patients on PPI it will not be clear whether their treatment dosage or regime is best for their situation. This calls for the need to improve GORD diagnostics. Prompt endoscopy for every patient with GORD symptomatology is not feasible due to the relatively low rate of diagnosing relevant findings and the limited capacity of endoscopy departments. One of the tools that might help is a prediction model supporting differential diagnosis, like the one presented in *chapter 6*. Such a score list could have several means. A proper indication could prevent initiating PPI treatment, could prevent long-term use by providing better grounds for tapering down medication use, and could improve the diagnostic sequel resulting in better treatment of complications. Combined efforts will be needed to generate a proper working model viable for primary care.

The Dutch Dyspepsia management guideline for primary care provides recommendations to initiate non-continuous therapy directly after 4 to 8 weeks of empirical PPI treatment. Our results, suggesting that pharmacological dependency was overestimated in at least 50% of chronic users without evidence-based indication, support this recommendation. Soon after initiation of treatment of GORD-like symptoms more information is available concerning the nature of complaints ('real' GORD or just incidental reflux symptoms), diagnostic procedures and response to

standard treatment. This will facilitate providing the patient with relevant information about non-continuous treatment and enhance patients' motivation. High effectiveness of on-demand treatment was found in studies with patients newly consulting with symptoms, when non-continuous treatment was started after 4 weeks of daily medication [3]. In these studies, placebo responses (often in combination with antacids) were also high. These studies therefore demonstrate that patients presenting for the first time with GORD-like symptoms can more easily be switched to non-continuous treatment, and that there is a large subgroup -probably with functional disease, short-term and/or self-limiting symptoms- receiving PPI treatment but not needing it at all.

With the aim to prevent patients from becoming a long-term user, patients with self-limiting or functional complaints should be discouraged from entering the medical circuit. This could perhaps be accomplished by providing PPIs over-the-counter (OTC). In 2002 the FDA approved Prilosec (Omeprazole 20 mg) as OTC medication for heartburn and acid regurgitation in the United States [4]. Out-of-pocket costs were shown to be an effective way in reducing PPI consumption [5]. With respect to safety, self-medication with Prilosec was shown to be accurately selected for heartburn and acid regurgitation, patients were shown to comply with the 14 days regime, and to appropriately seek physician involvement for longer-term management [6].

In both strategies described, adequate communication between patient and general practitioner is important. Proper information should be provided with respect to the disease and its history, the advised alternative treatment, goals, adverse side-effects of long-term use, risks of terminating treatment, problems the patient can encounter and how to anticipate these. This will require a time investment by the general practitioner or the nurse practitioner. Rather than during a personal consultation, information could also be provided via a personal letter or in a brochure the patient is handed over after the initial short-term treatment period. This information in combination with support is needed to motivate the patient for dosage reduction, or for terminating short-term treatment. Specifically with respect to long-term PPI therapy, it was shown that patients appreciate this kind of attention by their general practitioner, and would like to be more actively involved in treatment decisions and in achieving the minimal effective dosage; the magnitude of these aspects was underestimated by the general practitioner [7].

By applying these strategies, both general practitioners and patients could become more diligent to prescribing, finding and using the least effective dosage for symptomatic management of GORD. Together this should enable to implement the main result of the ELISE study in primary care practice.

REFERENCES

1. Gorgels WJ, Oude Voshaar RC, Mol AJ, van de Lisdonk EH, van Balkom AJ, van den Hoogen HJ, Mulder J, Breteler MH, Zitman FG. Discontinuation of long term benzodiazepine use by sending a letter to users in family practice: a prospective controlled intervention study. *Drugs Alcohol Depend* 2005;78:49-56.
2. Oude Voshaar RC, Gorgels WJ, Mol AJ, Couvée JE, van Balkom AJ, Zitman FG. Behandelmethoden om langdurig benzodiazepinegebruik te staken. *Ned Tijdschr Geneeskd* 2001;145:1347-1350.
3. Pace F, Tonini M, Pallotta S, Molteni P, Porro GB. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand'. *Aliment Pharmacol Ther* 2007;26:195-204.
4. Curtiss FR. OTC omeprazole for your heartburn: enormous value-for-money opportunity. *J Manag Care Pharm* 2005;10:458-460.
5. Mabasa VH, Johnny MA. Effect of a therapeutic maximum allowable cost (MAC) program on the cost and utilization of proton pump inhibitors in an employer-sponsored drug plan in Canada. *J Manag Care Pharm* 2006;12:371-376.
6. Fendrick AM, Shaw M, Schachtel B, Allgood L, Allgood G, Grender J, Peura D. Self-selection and use patterns of over-the-counter omeprazole for frequent heartburn. *Clin Gastroenterol Hepatol* 2004;2:17-21.
7. Grime J, Pollock K, Blenkinsopp A. Proton pump inhibitors: perspectives of patients and their GPs. *Br J Gen Pract* 2001;51:703-711.

SUMMARY

Gastro-oesophageal reflux disease (GORD) is a frequently occurring gastrointestinal disorder characterized by symptoms of heartburn and acid regurgitation. These symptoms can effectively be treated with acid suppressive medication (ASM), of which proton pump inhibitors (PPI) are nowadays more frequently used than histamine-2-receptor antagonists; 12% of the Dutch population uses ASM. Initial empirical short-term treatment often evolves in long-term treatment, due to fast, effective symptom resolution and high treatment satisfaction; 3% of the population chronically uses ASM. The majority of GORD patients in this group does not have an evidence-based indication for long-term daily medication intake, and therefore there is considerable overuse of ASM.
Since 2000, 'on-demand' therapy with ASM has been shown to be an effective and safe alternative in long-term treatment of uncomplicated GORD. Upon first occurrence of symptoms patients are treated for 4 to 8 weeks with a standard PPI dosage, and from then on only in case of recurrent symptoms using a patient-controlled intake pattern.

The aim of our research was to investigate whether long-term users of ASM for uncomplicated GORD are able to reduce or even terminate ASM treatment. An important aspect was to determine the effects of dosage reduction and temporal cessation of therapy on symptom control and quality of life. Secondly, we aimed to identify patient characteristics predicting a successful transfer from continuous therapy to dosage reduction. Finally, we evaluated the applicability of a prediction model that might help the general practitioner selecting the optimal treatment strategy for patients with GORD-like symptomatology.
Our research was based on a group of 288 primary care patients using long-term, continuous ASM for GORD, without an evidence-based indication for this use. In a randomized controlled trial they blindly adjusted the minimal dosage of ASM required to control their symptoms.

To gain insight in the group of patients we analyzed their baseline characteristics thereby focusing on factors influencing symptom control and the dosage used prior to study entry. *Chapter 2.1* shows the high prevalence of overweight (BMI ≥25) and obesity (BMI ≥30) in the patient group. It was already known that overweight is a risk factor for symptomatic GORD. We showed that the prevalence and severity of residual reflux symptoms in ASM-treated GORD patients were increased by overweight as well.

Therefore -in addition to medication- losing weight could aid in controlling reflux symptoms, and could prevent unnecessary dosage escalations.
An infection with *Helicobacter pylori*, the bacterium involved in etiology of peptic ulcers of the stomach, was diagnosed in 25% of our patients. There is evidence that *H. pylori* enhances the efficacy of ASM. Indeed, in *chapter 2.2* it was shown that infected patients need a lower dosage of ASM to control their reflux symptoms than uninfected patients. As eradication of *H. pylori* is advisable, treatment of an *H. pylori* infection in GORD patients could require a dosage increase to maintain a similar level of symptom control.
Psychological distress in untreated GORD patients is often described in literature. The psychological state and generic quality of life of our ASM-treated GORD patients were shown to be similar to the averages of the Dutch population *(chapter 2.3)*. It therefore seems that psychological distress is not inherent to the disease but related to its symptoms. We hypothesize that ASM benefits not only physiologically but also restores quality of life and psychological state.
To identify factors influencing inadequate symptom control in GORD patients despite ASM treatment, we compared patients who completely controlled their reflux symptoms on ASM with those who experienced residual symptoms (*chapter 3*). Regression analysis showed that residual symptoms were not related to lifestyle, dosage, or disease history; inadequate symptom control was associated with a disturbed psychological state. In the discussion a vicious circle is described in which psychological distress and symptoms reinforce each other. Management of psychological distress could be supportive in treatment of residual or recurrent symptoms in ASM-treated GORD patients.

The primary results of the ELISE trial, in which GORD patients adjusted the minimal dosage of ASM they need for symptom control, are described in *chapter 4*. Patients received two containers with 'medication', one for daily use and with 'rescue' medication (to be taken 'on-demand'). Patients randomized to group 1 received daily placebo and Pantoprazole (a PPI) as rescue medication; they titrated their dosage by only using rescue medication in case of symptom experience. Group 2 had Pantoprazole as daily medication and placebo as rescue; this group served as a control and to make patients unaware of their regime. During the study it appeared that of patients on daily placebo, 19% terminated PPI treatment, 33% managed with an intermediate dosage of 2 - 6 tablets per week, and 48% sustained their daily PPI dosage. At these adjusted dosages, symptom control and quality of life were dosage-independent, and furthermore equal to values of patients on fixed daily Pantoprazole. During the dosage adjustment process, 24% of patients experienced a temporal decrease in symptom control. We conclude that despite a history of long-term

continuous ASM treatment, patients are very well able to reduce their dosage and can therefore be switched from daily to on-demand treatment.
It would be very helpful for the general practitioner to be able to predict which patients on daily ASM can successfully reduce their dosage. Comparison of patients able to reduce their dosage (52% in our study) with those persisting in a daily dosage (48%) did not result in a clinically relevant prediction model (*chapter 5*). Successful dosage reduction by GORD patients remains a process of trial and error in which motivation of the patient and support by the physician will be important factors.
The first step in reducing non-indicated chronic PPI use is preventing patients from becoming a chronic user. In this respect a differential diagnosis of GORD, including the severity of disease, could be helpful. Distinguishing patients with non-erosive disease, with mild erosive- (oesophagitis A/B), and with severe erosive GORD (oesophagitis C/D/Barrett's) would aid in preventing chronic PPI use by patients belonging to the first two categories. These patients do not need PPI therapy, or can be stepped down after an empirical PPI trial. In *chapter 6* we explored the applicability of a prediction rule, containing eight patient-, symptom- and disease characteristics. A confirmed, differential diagnosis was obtained from over 1100 patients referred by their general practitioner for an upper gastrointestinal endoscopy (UGE) to the hospital. The prediction rule was able to discriminate patients with oesophagitis from those without erosions. Furthermore, two cut-off points were identified classifying the vast majority of patients correctly to non-erosive disease, oesophagitis A/B, and oesophagitis C/D/Barrett's. Therefore, the prediction rule proved to be useful as additional support in decisions like treatment options and UGE referral for patients with reflux symptoms in primary care.

In *chapter 7*, management strategies aimed at reducing unnecessary use of ASM are described. A minimal intervention strategy could be an efficient option. Patients, selected as in our study, can be contacted by their general practitioner via a personal letter advising them to switch to an on-demand regime. This letter should include suggestions to overcome rebound hypersecretion of gastric acid during the transition period, and provide information on when to contact the physician. Secondly, patients should be prevented from becoming an unnecessary chronic user. By means of a differential diagnosis of GORD early in the course of disease, initiation of PPI therapy can be postponed, and in case PPI therapy is indicated, on-demand treatment can be initiated directly after an empirical PPI trial.
These strategies should enable to reduce unnecessary use of ASM for uncomplicated GORD, and make general practitioners and patients more diligent to prescribing, finding and using the least effective dosage for symptomatic management of GORD.

SAMENVATTING

Gastro-oesofageale refluxziekte is een veel voorkomende aandoening die zich kenmerkt door zuurbranden en zure oprispingen. Deze symptomen worden behandeld met zuurremmende medicatie, waarvan de proton pomp remmers, zoals Omeprazol, tegenwoordig meer gebruikt worden dan histamine-2-receptor antagonisten, zoals Zantac; 12% van de Nederlandse bevolking gebruikt zuurremmers. Een kortdurende proefbehandeling met zuurremmers mondt vaak uit in langdurig gebruik vanwege snelle, effectieve klachtenverlichting en grote therapie tevredenheid; 3% van de bevolking gebruikt chronisch zuurremmers. Het merendeel van de refluxpatiënten binnen deze groep heeft geen aangetoonde indicatie voor langdurig, dagelijks gebruik: zuurremmers worden teveel en soms onnodig gebruikt.
Sinds 2000 zijn de effectiviteit en veiligheid aangetoond van de 'zo-nodig' behandeling van ongecompliceerde refluxziekte. De eerste symptomen worden behandeld voor een periode van 4 tot 8 weken met een standaard dosis zuurremmer, en vanaf dan worden alleen terugkerende klachten behandeld met een door de patiënt ingesteld patroon van medicatie inname.

De vraagstelling van ons onderzoek was of patiënten met ongecompliceerde refluxziekte die al langdurig maagzuurremmers gebruiken in staat zijn hun medicatie te minderen of zelfs te staken. Een belangrijk aspect hierin was in welke mate een dosisvermindering of het geheel staken van medicatie van invloed is op de klachtencontrole en kwaliteit van leven. Vervolgens hebben we gezocht naar patiëntkenmerken die kunnen voorspellen welke patiënten succesvol hun dosis kunnen verminderen. Tenslotte hebben we de praktische toepassingen van een voorspellingsmodel bekeken dat de huisarts zou kunnen helpen de optimale behandeling te kiezen voor patiënten met refluxachtige symptomen.
Het onderzoek is gebaseerd op 288 patiënten, uit huisartspraktijken, die langdurig zuurremmers gebruikten om refluxklachten te onderdrukken, zonder een indicatie voor deze mate van gebruik. In een gerandomiseerde klinische trial bepaalden zij 'blind' (zoveel mogelijk onbewust) de minimale dosis die ze nodig hadden om hun klachten onder controle te houden.

Om inzicht te krijgen in de patiëntengroep hebben we eerst hun kenmerken geanalyseerd met daarbij speciale aandacht voor factoren die van invloed zijn op de mate van klachtencontrole en de dosis zuurremming die gebruikt werd voorafgaand

aan de studie.
Overgewicht (body mass index (BMI) ≥25) en obesitas (BMI ≥30) kwamen veel voor in deze groep. Het was al bekend dat overgewicht de kans op het ontstaan van refluxziekte vergroot. Uit *hoofdstuk 2.1* blijkt dat overgewicht ook in refluxpatiënten die chronisch medicatie gebruiken de kans op, en de ernst van restklachten vergroot. Bij patiënten die ondanks medicatie hun klachten niet volledig onder controle hebben, zou afvallen kunnen bijdragen aan volledige onderdrukking van de klachten.
De bacterie *Helicobacter pylori* (veroorzaker van maagzweren) werd aangetoond bij 25% van de patiënten. Literatuurgegevens suggereren dat een infectie met *H. pylori* de werkzaamheid van maagzuurremmers versterkt. Inderdaad laat *hoofdstuk 2.2* zien dat geïnfecteerde patiënten een lagere dosis zuurremming nodig hebben voor hun refluxklachten dan niet-geïnfecteerde patiënten. Daar behandeling van een *H. pylori* infectie wenselijk is (ook bij patiënten zonder maagzweren), zouden refluxpatiënten na een kuur tegen *H. pylori* een hogere dosis zuurremming nodig kunnen hebben voor hun refluxklachten.
Psychoproblematiek bij onbehandelde refluxpatiënten wordt veelvuldig beschreven in de literatuur. De psychologische toestand en kwaliteit van leven van medicatie-behandelde refluxpatiënten bleek gelijk aan die van de Nederlandse bevolking (*hoofdstuk 2.3*). Het lijkt erop dat verminderd psychologisch welzijn niet gekoppeld is aan de aandoening op zich maar aan de klachten ervan, en dat bij vermindering van klachten psychologisch welzijn normaliseert.
Om factoren te identificeren die van invloed zijn op restklachten ondanks behandeling met zuurremmers, vergeleken we in *hoofdstuk 3* behandelde patiënten die hun klachten volledig onder controle hadden met patiënten die restklachten rapporteerden. Deze groepen verschilden niet met betrekking tot leefstijl, dosis en ziektekenmerken; het hebben van restklachten bleek wel geassocieerd met psychoproblematiek. Wij beschrijven een vicieuze cirkel waarin psychoproblematiek en symptomen elkaar versterken. Als er ondanks standaardbehandeling (episodes van) restklachten zijn, zou behandeling van psychoproblematiek behulpzaam kunnen zijn de refluxklachten onder controle te krijgen.

De resultaten van de ELISE trial, waarin de patiënten hun minimale dosis zuurremming voor klachtencontrole bepaalden, zijn beschreven in *hoofdstuk 4*. Patiënten kregen beschikking over twee potjes met 'medicatie', één voor dagelijks gebruik en één voor 'zo-nodig' gebruik. Groep 1 had placebo (een neppil) voor dagelijks gebruik en Pantoprazol (een proton pomp remmer) voor 'zo-nodig'; deze patiënten titreerden hun dosis door alleen uit het 'zo-nodig' potje te gebruiken als ze klachten ondervonden. Groep 2 kreeg dagelijks Pantoprazol en had placebo als 'zo-

nodig'; deze groep diende als controle en om de patiënten onbewust te maken van wat er in de potjes zat. Gedurende de studie bleek van de patiënten die dagelijks placebo kregen, 19% te stoppen met het gebruik van de zuurremmer, 33% hun dosis te reduceren naar 2-6 tabletten per week, en 48% dagelijks medicatie te blijven gebruiken. Op deze ingestelde dosis was onderdrukking van de klachten onafhankelijk van de gebruikte dosis, en bovendien gelijk als voor patiënten die een dagelijkse dosis kregen. Gedurende het instellen van de dosis ondervond 24% van de patiënten een tijdelijke verslechtering van de klachten. De conclusie van de studie is dat ondanks een historie van langdurig gebruik van zuurremming, patiënten goed in staat zijn tot dosisvermindering, en daarom hun medicatie 'zo-nodig' kunnen gaan gebruiken.

Voor de huisarts zou het handig zijn om aan de hand van een aantal patiëntkenmerken te kunnen voorspellen wie met succes 'zo-nodig' kan gaan gebruiken. Na het vergelijken van patiënten die wel (52%) en niet (48%) in staat waren hun dosis te verminderen, gaven deze data geen aanwijzingen voor een klinisch toepasbaar voorspellingsmodel (*hoofdstuk 5*). Succesvolle dosisvermindering door refluxpatiënten blijft daarom een kwestie van proberen; gedurende dit proces zullen motivatie van de patiënt en steun door de huisarts belangrijk zijn.

Om niet-geïndiceerd langdurig gebruik van maagzuurremmers te verminderen, is het voorkomen van chronisch gebruik de eerste stap. Hierbij zou een differentiële diagnose naar de ernst van refluxziekte behulpzaam kunnen zijn. Onderscheid tussen patiënten zonder ontstekingen van de slokdarm, met milde- (oesofagitis graad A/B), en met ernstige- (oesofagitis graad C/D) en premaligne afwijkingen, voorkomt dat patiënten uit de eerste twee categorieën chronisch gaan gebruiken. Voor hen voldoet een kortdurende proefbehandeling die afgebouwd kan worden. In *hoofdstuk 6* hebben we de toepassing van een voorspellingsregel (gebaseerd op acht patiënt-, symptoom- en ziektekenmerken) onderzocht, door voor ruim 1100 patiënten die zich bij hun huisarts meldden met refluxachtige klachten zo'n differentiële diagnose te verkrijgen door middel van een gastroscopie in het ziekenhuis. Met de voorspellingsregel bleek de meerderheid van de patiënten correct geclassificeerd te worden in één van de bovengenoemde drie categorieën. De voorspellingsregel zou de huisarts behulpzaam kunnen zijn bij het kiezen van de juiste behandelingsstrategie (geen, kort, lang) en in de beslissing voor het verwijzen voor gastroscopie.

In *hoofdstuk 7* beschrijven we praktische mogelijkheden die gebruikt kunnen worden om onnodig gebruik van maagzuurremmers te verminderen. Een minimale interventiestrategie zou een effectieve mogelijkheid kunnen zijn. De huisarts kan patiënten selecteren op dezelfde manier als gedaan in onze studie, en deze patiënten

vervolgens persoonlijk aanschrijven. Via deze brief wordt geadviseerd ‘zo-nodig’ te gaan gebruiken en wordt informatie gegeven hoe dit gelijkmatig te doen, en bij welke problemen contact op de nemen met de arts. Ten tweede, door middel van een differentiële diagnose van refluxziekte kan therapie met proton pomp remmers worden uitgesteld of kan, als therapie wel moet worden gestart sneller aangevangen worden met een ‘zo-nodig’ behandeling.

Door gebruik te maken van deze strategieën zou het mogelijk moeten zijn om onnodig gebruik van maagzuurremmers door patiënten met refluxklachten te verminderen, en zullen zowel patiënten als huisartsen zich inzetten om een minimale effectieve dosis te vinden, en voor te schrijven.

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CURRICULUM VITAE

Alike van der Velden, geboren 15 juli 1968, te Maarn.

1980-1987	VWO, Het Christelijk Lyceum, Zeist.
1987-1993	Biologie, medische richting, Universiteit Utrecht.
1990-1991	Stage bij de vakgroep Moleculaire Celbiologie (Prof. dr. H.O. Voorma): B-cell and T-cell epitopes on the Haemagglutinin protein of Measles virus.
1991-1992	Stage bij de vakgroepen Experimentele Pathologie en Gynaecologie (Prof. dr. A.P.M. Heintz): Rejection of murine ovarian teratocarcinoma after treatment with cisplatin and Interleukin-2.
1992-1993	Stage bij het Institute for Animal Health, Pirbright, UK (Dr. G.J. Belsham): Defective point mutants of the Encephalomyocarditis virus internal ribosome entry site can be complemented *in trans*.
1993	Doctoraal examen.
1993-1994	Onderzoek bij de vakgroep Antropogenetica, Vrije Universiteit, Amsterdam (Dr. H. Joenje): Expression cloning of Fanconi anaemia genes.
1995-1999	Promotie-onderzoek bij de vakgroep Moleculaire Celbiologie, Universiteit Utrecht (Prof. dr. H.O. Voorma, co-promotor: Dr. A.A.M. Thomas): Translation initiation and control by the 5' untranslated region of the mRNA.
1999	Transgenese project bij het Hubrecht laboratorium (Dr. O.H.J. Destrée).
2000-2003	Onderzoeks- en kwaliteitsmedewerker bij Leja Research, Nieuw-Vennep.
2003-2007	Promotie-onderzoek bij het Julius Centrum voor Gezondheids-wetenschappen en Eerstelijns Geneeskunde, Universitair Medisch Centrum Utrecht (Prof. dr. D.E. Grobbee, co-promotor: Dr. M.E. Numans): Long-term treatment of gastro-oesophageal reflux disease in primary care.
2007-	Onderzoeker bij het Julius Centrum (Prof. dr. T.J.M. Verheij, Dr. M.M. Kuyvenhoven): Implementation of a multiple intervention aimed at optimizing prescription of antibiotics for respiratory tract infections, embedded within the new practice accreditation of the Dutch college of general practitioners: a randomized controlled trial (ARTI4).

PUBLICATIONS

MANUSCRIPTS BASED ON THIS THESIS

Van der Velden AW, de Wit NJ, Quartero AO, Grobbee DE, Numans ME. Maintenance treatment for GERD: residual symptoms are associated with psychological distress. *Digestion* 2008;77:207-213.

Van der Velden AW, de Wit NJ, Quartero AO, Grobbee DE, Numans ME. GORD patients on chronic acid suppressive medication: a population-average psychological state. *Scand J Gastroenterol, in press*.

Van der Velden AW, de Wit NJ, Quartero AO, Grobbee DE, Numans ME. Pharmacological dependency in chronic treatment of GORD: a randomized controlled clinical trial. *In revision, Aliment Pharmacol Ther*.

Van der Velden AW, Quartero AO, de Wit NJ, Grobbee DE, Numans ME. GORD patients on chronic acid suppressive medication: overweight impairs symptom control. *Submitted*.

Van der Velden AW, de Wit NJ, Quartero AO, Grobbee DE, Numans ME. GORD patients on chronic acid suppressive medication: *Helicobacter pylori* infection reduces medication necessity.

Van der Velden AW, de Wit NJ, Quartero AO, Grobbee DE, Numans ME. Patient selection for on-demand PPI therapy after chronic treatment of GORD: trial and error.

Van der Velden AW, Numans ME. Supporting differential diagnosis of GORD with weighed patient characteristics in primary care.

OTHER PUBLICATIONS

Bernsen MR, van Barlingen HJ, van der Velden AW, Dullens HF, den Otter W, Heintz AP. Dualistic effects of cis-diammine-dichloro-platinum on the anti-tumor efficacy of subsequently applied recombinant Interleukin-2 therapy: a tumor-dependent phenomenon. *Int J Cancer* 1993;54:513-517.

Van der Velden A, Kaminski A, Jackson RJ, Belsham GJ. Defective point mutants of the Encephalomyocarditis virus internal ribosome entry site can be complemented *in trans*. *Virology* 1995;214:82-90.

Bernsen MR, van der Velden AW, Everse LA, Dullens HF, den Otter W, Heintz AP. Interleukin-2: hope in cases of cisplatin-resistant tumours. *Cancer Immunol Immunother* 1998;46:41-47.

Van der Velden AW, Thomas AAM. The role of the 5' untranslated region of an mRNA in translation regulation during development. *Int J Biochem Cell Biol* 1999;31:87-106.

Van der Velden AW, Destrée OHJ, Voorma HO, Thomas AAM. Controlled translation initiation on Insulin-like growth factor 2-leader 1 during *Xenopus laevis* embryogenesis. *Int J Dev Biol* 2000;44:843-850.

Van der Velden AW, Los A, Voorma HO, Thomas AAM. Sequence and translation initiation properties of the *Xenopus* TGFβ5, PDGF-A, and PDGF-α receptor 5' untranslated regions. *Int J Dev Biol* 2000;44:851-859.

Van der Velden AW, Voorma HO, Thomas AAM. Vector design for optimal protein expression. *Biotechniques* 2001;31:572-582.

Van der Velden AW, van Nierop K, Voorma HO, Thomas AAM. Ribosomal scanning on the highly structured Insulin-like growth factor II-leader 1. *Int J Biochem Cell Biol* 2002;34:286-297.