Genetic and psychological determinants of dyspepsia and implications for treatment

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‘Genetic and psychological determinants of dyspepsia and implications for treatment’

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Genetic and psychological determinants of dyspepsia and implications for treatment

Genetische en psychologische determinanten van dyspepsie en de implicaties voor de behandeling

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

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Contents

Chapter 1

General introduction

Suhreta Mujakovic

Epidemiology

Dyspepsia is a very common condition in the population with a prevalence ranging from 25 to 40% (1). It refers to a complex of symptoms believed arising in the upper gastrointestinal tract and includes heartburn, acid regurgitation, excessive burping or belching, a feeling of slow digestion, early satiety, nausea and bloating (2). Dyspepsia is an important and costly health problem due to high medical costs for diagnostic investigations (3) and for drug treatment (4) and its impact on absenteeism from work (5).

The proportion of people who seek medical attention due to dyspepsia in primary care ranges from 3% to 8% (6-8). Only a fraction of these patients is referred to secondary care for further clinical investigation such as endoscopy (8), about 20% in one year follow-up (9). The majority of the dyspeptic patients is managed in primary care without further diagnostic work-up. This group is referred to as uninvestigated dyspepsia.

Aetiology

The aetiology of dyspepsia is very complex and still poorly understood. Several causal factors are suggested: Helicobacter pylori infection, excessive gastric acid, delayed gastric emptying, visceral hypersensitivity, psychosocial morbidity, use of NSAID's and post-infective mucosal damage. Recently also genetic predisposition has been suggested as a relevant factor in the genesis of dyspeptic complaints.(10-14) A distinction can be made between organic dyspepsia (e.g. reflux-oesophagitis, peptic ulcer disease) and functional dyspepsia (no detectable tissue damage at diagnostic work-up). In the majority of the patients (50-70%) no organic causes for the symptoms are found.

Current treatment options and recommendations

Several treatment options exist for uninvestigated dyspepsia. The choice depends on the age and the clinical presentation. If there is a reason to suspect malignancy clearly endocopy is indicated. In other cases treatment will typically exist of life style advices and/ or treatment with antacid or H2 Receptor Antagonist (H2RA). Patients with uninvestigated dyspepsia and recurrent symptoms are usually tested and treated for Helicobacter pylori or empirically treated with proton pump inhibitors (PPI) (15).

Unfortunately only about 50% of the patients with uninvestigated dyspepsia experiences effective symptom relief with acid inhibiting drugs, prokinetics or (tricyclic) antidepressants
(16). Psychological distress, personality and psychiatric disturbances are likely to play a role in poor treatment outcome of dyspepsia. (16-20) Elevated levels of distress are not only associated with treatment failure but, also with recurrence and exacerbation of dyspeptic symptoms and with frequent health care seeking (21).

Dyspepsia, personality and psychiatric disturbances

Psychological factors such are personality traits and psychiatric disorders have significant effects on dyspepsia. Firstly, they are more common in dyspeptics than in healthy subjects. Population based studies found that psychiatric co-morbidity and especially anxiety and mood disorders are over represented in dyspeptics (22-24). Secondly, they may affect symptoms or at least symptom experience. Psychological stress or distress is repeatedly found to be associated with severe dyspepsia. Individuals suffering from chronic stress are more prone to experience exacerbation of dyspeptic symptoms (25). Thirdly, they influence treatment outcome. It is still uncertain in which way psychological and psychiatric factors affect treatment outcome. Personality traits were found to be associated with poor treatment outcome (20) and psychological problems such are anxiety and somatisation are associated with successful treatment (26). Fourthly, they affect healthcare consumption. Frequent consultation and symptom recurrence are more often observed in patients with psychosocial co morbidity (27).

Dyspepsia and genes

The role and importance of genes in the pathogenesis of dyspepsia remains to be determined (28). Until now an association with upper abdominal symptoms (dyspepsia) has only been found for the homozygous C genotype of the C825T polymorphism in the gene encoding the G protein ß3 subunit (14). Genes of the serotonergic system such as various serotonin receptors and serotonin reuptake transporter (SERT), have been proposed as candidate genes (29). Of all serotonin 90% is present in the GI tract, where it modulates gastrointestinal sensitivity and motility. Until now very few studies have been performed to assess the association between genes of serotonergic system and dyspepsia. Pharmacological studies (30;31) showed that patients suffering from diarrhoea predominant IBS (HTR3

antagonist) and patients with constipation predominant IBS (HTR4 agonist) experience symptom relief on antagonists and agonists of serotonin receptors 3 and 4 respectively trough their influence on gut motility and sensitivity.

Aim of this thesis

The main aim of this thesis is to investigate psychosocial, personality and genetic factors related to dyspepsia that might affect symptom severity and the effectiveness of current treatment. The objectives of this thesis are: **a)** to give an systematic overview of the association between psychopathology, personality traits, coping styles, major life events and dyspepsia in an systematic review and meta-analysis, **b)** to investigate the association between psychopathology, coping style, major life events and severity of dyspeptic symptoms in a population of primary care patients with dyspepsia, **c)** to investigate the contribution of the CYP2C19 genotype to treatment success in subset of patients treated with PPI as a initial treatment strategy, **d)** to investigate whether there is an association between HTR3A C178T genotype and dyspeptic symptoms, **e)** to investigate which empirical treatment strategy step-up or step-down is most effective and efficient in the treatment of uninvestigated dyspepsia, **f**) to explore which factors, either gastrointestinal, psychological, demographic or biological, determine short treatment success with antacids and PPI, and which factors determine long treatment failure. Finally, psychosocial, personality and genetic factors and their effect on dyspeptic symptom severity and effectiveness of current treatment are discussed.

Study population in the DIAMOND study

This study was part of the DIAOMOND study (Dutch study on InitiAl Management Of Newly diagnosed Dyspepsia) in which the effectiveness of a step-up versus step-down treatment strategy in uninvestigated dyspepsia was studied. DIAMOND is a multicenter study with three participating universities (UMC Utrecht, St Radboud Nijmegen and UMC Maastricht) and 127 general practices in central and southern part of the Netherlands participating.

Patients included in the DIAMOND study (n=664) were aged 18 years and older, consulting their general practitioner for (new) onset of dyspepsia and were able to fill out the Dutch questionnaires. Eligible patients were randomly assigned to step-up or step-down treatment arm. At the baseline, patient filled out questionnaires regarding dyspeptic symptoms, demographic data, psychological state, coping style,

major life events, quality of life and compliance. During the follow-up period of six months, questionnaires regarding dyspeptic symptoms were sent at 2 weeks (T1), after ending each treatment step or at intervals of 4 weeks (T2, T4, T6), and at six months (T7). In case of relapse within the 4 weeks of treatment an additional questionnaire was sent to assess the dyspeptic symptoms state (T3, T5).

Outline of this thesis

In Chapter 2 we describe the results of a systematic review and meta-analysis on the association between psychosocial factors and dyspepsia. We compared outcomes of the studies investigating one of the following topics: psychopathology, personality disturbances, major life events and coping ability in dyspeptic patients and healthy controls.

In Chapter 3 we describe the relationship between psychopathology measured with symptom checklist-90, coping style, major life events and dyspeptic symptom severity in 664 primary care patients with uninvestigated dyspepsia.

In Chapter 4 we present the results of an analysis of the relative influence of CYP2C19*2 genotype on treatment success in 319 patients starting with PPI as initial treatment of dyspepsia. Hepatic metabolism of PPI is dependent on CYP(450)2C19 enzyme. Genetic polymorphism in CYP2C19 creates slower metabolisation of proton pump inhibitors.

In Chapter 5 we describe the association study between functional polymorphisms in serotonin receptor HTR3a (C187T) and 44 bp insertion/deletion polymorphism in serotonin reuptake transporter (SERT) and dyspeptic symptoms (severity).

In Chapter 6 we report on the outcome of the DIAMOND trial, and analyse the cost-effectiveness of the step-up versus step-down treatment strategy in univestigated dyspepsia.

In Chapter 7 we present the results of the study on determinants of successful short term success therapy with antacids on one hand and PPI treatment on the other. Furthermore, determinants of long term therapy failure are described.

In Chapter 8 we discuss how psychopathology, coping style, major life events and genes influence the severity of dyspeptic symptoms and ultimately the outcome of acid inhibitory treatment.

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Chapter 2

Psychiatric and personality factors in dyspepsia: a systematic review and meta-analysis

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D.E. Grobbee, M. Samsom & N. J. de Wit

Abstract

Background: A number of studies have addressed the possible relation between dyspepsia and psychological and psychiatric disturbances but results were inconsistent. We explored the association between dyspepsia and (a) personality traits, (b) psychiatric disorders, (c) major life events, and (d) coping ability in detail, using systematic review and meta-analysis.

Methods: Medline and Embase databases were systematically searched for relevant MeSH terms from 1978 until 2006. The studies were screened for quality and eligibility, for a clearly defined patient group with dyspepsia, for comparison with a control group, and for validated outcome measurements. Results were pooled and binary data were analysed separately from continuous data.

Results: One hundred and fifty-three studies were identified and 27 were found suitable for data extraction. The odds ratio for anxiety (4 studies; n=4) and depression (n= 4) in dyspeptic patients was 1.57 (95% CI 1.01 to 2.45) and 2.84 (95% CI 1.89 to 4.25) compared to the control group. In studies with continuous data, dyspepsia was significantly associated with personality traits [anxiety (n= 8), neuroticism (n= 10) and somatisation (n= 5)] as well as with psychiatric disorder [anxiety (n= 7), and depression (n= 14),]. Dyspeptic patients used less appropriate coping skills in stressful situations compared with controls (n= 3), and had more major life events in their recent history (n=5, pooled OR 1.94 (95% CI 1.27-2.96).

Conclusions: This meta-analysis supports the hypothesis that personality and psychiatric factors are indeed involved in the aetiology of dyspepsia. More clearly defined prospective studies are needed to explore the clinical consequences of our findings.

Introduction

Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are among the most common functional gastrointestinal disorders (FGID) (1, 2). Dyspepsia describes a symptom complex thought to arise in the upper gastrointestinal tract and includes symptoms such as heartburn, acid regurgitation, excessive burping or belching, a feeling of slow digestion, early satiety, nausea and bloating (3).The prevalence ranges from 25-40% worldwide (4). The proportion of people with dyspeptic complaints who seek medical attention in primary care ranges from 3% to 8% (5-7). Of these, only about 13% is referred to secondary care for further clinical investigation such as endoscopy (8). After diagnostic evaluations, in the majority of dyspeptic patients no structural organic disease is found and they are usually classified as having functional dyspepsia (9).
In view of the absence of clear organic causes, the question why so many people have dyspeptic symptoms still remains unanswered. Gastric acid, Helicobacter pylori infection, delayed gastric emptying, visceral hypersensitivity, psychosocial morbidity, and post-infective mucosal damage are possible factors implicated in the development of dyspepsia (10-13).

In many patients, psychiatric disease or psychosocial problems coincide with the gastro-intestinal (GI) complaints (14-18).
It has been generally accepted that psychological stress represents an important risk factor in aetiology of dyspepsia and also of many other diseases (19-21).
Moreover, several studies reported that psychosocial and environmental stress may affect GI motility, as well as stomach sensitivity (22-24). Major life events (MLE), notably negative events such as losing a loved one or serious illness, can cause high level of stress. Dyspeptic patients are reported to experience more negative life events compared to healthy controls and they may use less favorable coping skills (25-28).

Even though many studies illustrate that dyspeptic patients have a higher burden of psychosocial and psychiatric co morbidity (26, 28, 29), the causal contribution of psychiatric and psychological factors to (functional) dyspepsia remains unclear. In order to get further insight in the clinical relevance of this association, we conducted a systematic review and meta-analysis of the available literature on the quantitative

relationship between dyspepsia and psychiatric factors, major life events, and coping style.

Methods

Search strategy

Studies published from January 1978 until September 2006 were identified on the basis of a structured literature search in Medline and Embase databases. "Dyspepsia" was used as MeSH Major Topic and it was combined using the Boolean operator AND with the following MeSH terms: "Mental disorders", "Life change events", "Stress psychological", "Psychology" and "Adaptation psychological".

The search was restricted to articles published in the English language. References of reviewed articles were searched for additional articles missed by the database search.

Study selection

Case-control and cross-sectional population studies, were selected for this review. Studies were screened for inclusion based on the following criteria:

- Clearly defined patient group (using diagnostic criteria for dyspepsia including validated questionnaires and endoscopic findings), and control group
- Personality traits, psychiatric disease (categorized as disorders or measured psychometrically), major life events (measured as number of events in patient and control group) and coping ability (measured psychometrically) are truly studied,
- Statistical parameters and data are reported that can be extracted to be incorporated in a meta-analysis.

Data extraction and quality assessment

Eligibility and quality of the studies as well as data extraction is done by 3 authors independently (SM, NdW, MN). The following data were extracted: number of patients and controls, assessment of dyspeptic symptoms, mean score and standard deviation on scales measuring: personality traits, psychiatric disease, major life events, and coping ability. Consensus was achieved for all data.

The quality of papers was assessed using a criteria list for assessment of case – control studies (30). This instrument includes 10 items about description of patient

and control groups, appropriateness of each measurement instrument, selection bias and exclusion of confounders, and validity and applicability to different health care settings (primary, secondary). According to these criteria the quality of each study was classified as follows:

High: all or all but one of the criteria were met

Medium: 2 or 3 criteria were not met

Low: 4 or more criteria were not met.

In the tables (results section) quality is represented by A=high quality, B=medium quality, C= low quality.

Data synthesis and analysis

The included studies were divided into four subcategories according to the subject studied: personality traits, psychiatric disease, coping style, and major life events. All data were used exactly as they were reported in the original article. All results of the selected studies were entered into The Cochrane Collaboration Review Manager and analysed using RevMan 4.2.8.(30). When the same outcome was measured with different scales the results were standardized to a uniform scale before combining. When only the confidence interval (CI) or standard error (Se) was reported in the original article, the value of the standard deviation (SD) was calculated.

We used a standardized mean difference (SMD) method (Hedge's adjusted g) to calculate effect size for data with continuous outcome (31). A SMD of zero means that there is no difference between the dyspepsia group and the control group. By convention a small effect size would be ≤ 0.2 standard deviation units (SDU), a medium effect size would be 0.5 SDU and ≥ 0.8 SDU would be a large effect size.

Homogeneity of effect sizes was calculated using chi-square (Q) statistic. Heterogeneity is assumed when the p-value of the test was <0.10 (32). In the situation when heterogeneity was present random effect model (REM) is used to calculate effect size. In these cases in stead of calculating one effect size for all studies (which could be potentially misleading) the mean of the distribution of effect and its variance are estimated (33; 34). Studies with very different outcome measures, which were not possible to pool in meta-analysis, were pooled using narrative synthesis.

Results

Search

The literature search identified 154 potentially relevant studies. Initially 79 were excluded on following grounds: 26 studies were reviews, for 28 studies the abstract was not available, 8 studies were not published in English language and 17 studies were not published as a journal article (e.g. letters, case reports, and editorials). The remaining 75 were assessed for eligibility. From those, 48 were excluded because they did not meet the agreed selection criteria, leaving us with 27 studies suitable for analysis (Figure 1 and Table 1).

Quality assessment

Quality assessment of the selected studies led to the following results: 6 out of 27 studies were classified as high quality, 11 studies were classified as medium quality and 10 studies were of low quality.

Study characteristics

Psychiatric disorder

The pooled results on anxiety syndrome (48-50, 52) and depression disorder (42, 49, 50, 52) are shown in Table 2 and Figure 2 and 3 respectively. Risks of presence of anxiety (OR= 1.57 95%CI 1.01- 2.45), as well as depressive disorder (OR=2.84 95%CI 1.89- 4.251) were significantly increased. There was no significant heterogeneity ($p>0.35$).

Figure 4 and table 2 show the risk of any psychiatric disorder (OR= 4.54 95% CI 2.12- 9.69). Across the four studies reporting on this outcome there was, however, marked heterogeneity ($p<0.001$).

Fourteen studies (14, 25, 27, 35, 41, 44, 46, 47, 49, 50, 53, 54, 56) reported a mean score on depression questionnaires and seven of these also reported a mean score on anxiety (25, 27, 35, 41, 53, 54, 56) questionnaires (Figure 6 and 7 and table 2). The results were very heterogeneous ($p<0.1$), but the pattern of the distribution of the results was very similar across the individual studies. They were all pointing in same direction with mean distribution of 0.62 standard deviation units (SDU) and 95%CI 0.44-0.79 for depression scores and for anxiety scores mean distribution was 0.58 SDU with 95%CI 0.28-0.88. The magnitude of the effect sizes was medium.

Figure 1. Flow diagram of studies identified by search

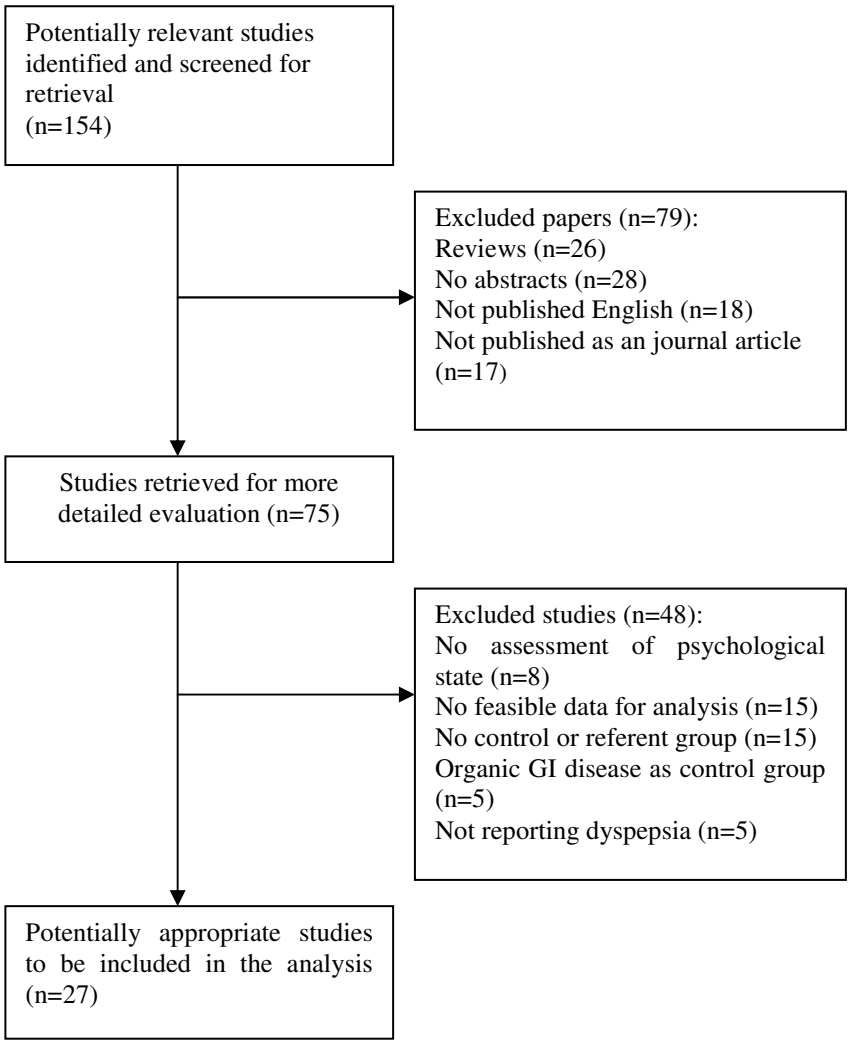


Table 1: Characteristics of included studies.

	Year	Design	Qual.	Domain	No. of sub-jects	No. of con-trols	Assessment of dyspepsia	Assesment of personality and psychiatric factors
Baker 39)	1995	Case-control	M	Pers/ Psy	51	43	Endoscopy	SCL-90-R, BDI, STAI, EPI
Bennett (25)	1991	Case-control	M	MLE, Pers/ Psy, Coping	62	62	Endoscopy	STAI, CES-D, EPI, LEDS
Cheng (28)	1999	Case-control	M	Coping	30	30	Endoscopy	CFIS
Chou (40)	2001	Case-control	L	Psy	39	18	Rome criteria	SDS
Hafeiz (41)	1997	Case-control	H	MLE	163	163	Endoscopy/ abd. sonography	LES
Haug 1993(29)	1993	Case-control	M	Psy	100	100	Endoscopy	DSM-III-R
Haug 1994(14)	1994	Case-control	M	Pers	21	17	>3 months to upper GI symptoms	BDI, STAI-Tr, EPQ-N, GHQ
Haug 1995(27)	1995	Case-control	M	Pers/Psy	100	100	Endoscopy	EPQ-N, STAI, BDI
Herschbach(42)	1999	Cross-sectional	L	Psy	288	1913	Research diagnostic questions for FGD	SCL-90/ depression/ somatisation
Hui (43)	1991	Case-control	M	MLE	33	33	Endoscopy	LES/ hassles scale
Jain (44)	1995	Case-control	L	Pers/Psy	35	45	Endoscopy	MHQ
Jonsson (45)	1995	Case-control	H	Pers/ Psy	25	25	GSRS	SCL-90, DSM-III-R
Kane (46)	1993	Case-control	L	Psy	210	68	Not clear	SADS-LA, BSI
Kok (47)	1989	Case-control	L	Pers/ Psy/ MLE	23	23	Endoscopy	EPQ, ZDS, DSM-III
Lee (33)	2000	Case-control	M	Pers/ Psy/ Coping	30	30	<1 months to upper GI symptoms	SCL-90, BDI, STAI, Ways of coping
Li 1(48)	2002	survey	L	Pers/ Psy	239	777	Rome II	ZDS, ZAS
Li 2 (48)	2002	Case-control	L	Pers/ Psy	72	197	Rome II	ZDS, ZAS

Locke (49)	2004	Case-control	M	MLE	47	119	BDQ questionnair	Life threatening events
Malt 2000 (50)	2000	Case-control	M	Psy	18	49	>3 months upper GI sympyoms	ICD-10
Malt 2003(51)	2003	Case-control	H	Psy	15	47	>3 months upper GI symptoms	Gottschalk and Bechte scoring sysytem
Norton (52)	1999	Cross-sectional	L	Pers/ Psy	29	98	Research diagnostic questions for FGD	BAI, BDI
Stanghellini(53)	1999	survey	M	Psy	1566	4015	Interview (DIGEST)	PGWBI
Talley(54)	1986	Case-control	H	Pers/ Psy	76	76	Endoscopy	EPI, C-C, BDI, STAI
Talley(55)	1987	Case-control	H	MLE	68	68	Endoscopy	LES
Talley 1(56)	1988	Case-control	M	Pers	50	50	Endoscopy	CECS
Talley 2(56)	1988	Case-control	M	Pers	31	32	Endoscopy	CECS
Talley(57)	1998	survey	M	Pers	65	133	Rome criteria	GHQ, EPQ
Tanum 1(58)	1999	Case-control	H	Pers	40	39	Endoscopy	EPQ, NEO-PI

Table 2: (Pooled) odds ratios and standardized mean differences of studies per domein

	Study	Dyspepsia	Control	OR	(95%CI OR)
Anxiety	Malt 2000	8/18	13/49	2.22	0.72-6.83
	Kane	86/210	24/68	1.27	0.72-2.24
	Kok	2/23	0/23	5.47	0.25-120.4
	Li(2)	2/72	3/197	1.85	0.30-11.29
	Li (1)	5/239	8/777	2.05	0.67-6.34
	Pooled	**103/ 562**	**48/1114**	**1.57**	**1.01-2.45**
Depression	Malt 2000	8/18	8/49	4.1	1.24-13.60
	Chou	21/39	0/18	43.0	2.42-763.9
	Kok	3/23	1/23	3.30	0.32-34.35
	Li(2)	34/72	50/197	2.63	1.50-4.62
	Li (1)	26/239	37/777	2.44	1.45-4.12
	Pooled	**92/391**	**96/1064**	**2.84**	**1.89-4.25**
Any psychiatric diagnosis	Haug 1993	35/100	1/100	53.31	7.13-398.75
	Malt 2000	12/18	21/49	2.67	0.86-8.27
	Li(3)	37/239	55/777	2.40	1.54-3.75
	Stanghellini	149/1566	76/4015	5.45	4.11-7.23
	Pooled	**233/1923**	**76/4015**	**4.54**	**2.12-9.69**
Major life events	Hafeiz	158/163	148/163	3.2	1.14-9.03
	Talley 1986	58/68	57/68	1.12	0.44-2.84
	Hui	27/33	23/33	1.96	0.62-6.21
	Locke 2004	26/47	49/119	1.77	0.90-3.50
	Kok	8/23	3/23	3.56	0.80-15.72
	Pooled	**277/334**	**280/406**	**1.94**	**1.27-2.96**

	Study	Dyspepsia	Control	SMD	(95%CI SMD)
		Mean (sd)	**Mean(sd)**		
Depression score	Norton	9.28 (6.54)	8.40 (6.54)	0.13	-0.28-0.55
	Li(1)	39.30 (8.10)	37.0 (7.30)	0.31	0.16-0.45
	Jain	5.40 (2.90)	4.50 (2.30)	0.35	-0.10-0.79
	Jonsson	0.36 (0.38)	0.24 (0.22)	0.38	-0.18-0.94
	Talley	6.84 (6.33)	4.72 (4.39)	0.39	0.07-0.71
	Beker	10.31 (6.82)	7.44 (6.51)	0.43	0.02-0.84
	Li(2)	47.0 (10.80)	42.0 (10.80)	0.46	0.19-0.73
	Herschbach	0.51 (0.56)	0.29 (0.44)	0.48	0.36-0.61
	Malt 2003	5.89 (0.97)	5.09 (1.21)	0.68	0.09-1.28
	Haug 1995	9.00 (7.20)	3.90 (4.20)	0.86	0.57-1.15
	Haug 1994	11.40 (9.40)	4.10 (4.20)	0.95	0.27-1.63
	Bennett	15.10 (10.9)	6.30 (6.40)	0.98	0.61-1.35
	Lee	28.40 (8.02)	17.58 (6.40)	1.47	0.90-2.05
	Kok	40.39 (7.96)	27.39 (5.94)	1.82	1.12-2.52
	Pooled			**0.62**	**0.44-0.79**
Anxiety score (state)	Malt 2003	1.98 (0.73)	1.73 (0.49)	0.44	-0.14-1.03
	Talley 1986	33.70 (10.94)	29.53 (7.99)	0.43	0.11-0.75
	Baker	34.35 (11.31)	30.67 (9.87)	0.34	-0.07-0.75
	Bennett	40.60 (11.40)	30.30 (6.30)	1.11	0.73-1.49
	Haug 1995	38.00 (10.0)	29.00 (6.0)	1.09	0.79-1.38

	Lee	49.87 (9.56)	48.41 (9.60)	0.15	-0.36-0.66
	Norton	12.24 (8.99)	9.28 (8.60)	0.34	-0.08-0.76
	Pooled			**0.58**	**0.28-0.88**
Trait anxiety	Baker	36.23 (10.89)	33.16 (10.09)	0.29	-0.12-0.70
	Bennett	41.90 (9.80)	33.80 (8.0)	0.90	0.53-1.27
	Haug 1994	41.10 (13.80)	30.00 (7.80)	0.94	0.27-1.62
	Haug 1995	40.0 (10.0)	32.0 (8.0)	0.88	0.59-1.17
	Lee	49.17 (8.29)	48.47 (7.43)	0.09	-0.42-0.59
	Talley 1988	18.90 (5.20)	18.10 (3.90)	0.17	-0.32-0.67
	Talley 1988	18.40 (4.80)	16.60 (4.60)	0.38	-0.02-0.78
	Talley 1986	36.67 (9.69)	33.07 (8.74)	0.39	0.07-0.71
	Pooled			**0.51**	**0.28-0.70**
Somatisation	Jonsson	0.49 (45.00)	0.18 (0.17)	0.01	-0.54-0.56
	Herschbach	0.69 (0.54)	0.37 (0.43)	0.72	0.59-0.84
	Baker	66.92 (11.10)	57.09 (11.64)	0.86	0.43-1.28
	Jain	7.80 (3.40)	4.10 (3.40)	1.08	0.60-1.55
	Lee	65.17 (7.92)	52.33 (9.24)	1.47	0.90-2.05
	Pooled			**0.82**	**0.48-1.16**
Neuroticism	Talley 1986	10.76 (5.44)	7.71 (4.98)	0.58	0.24-0.92
	Tanum 2001	10.30 (5.2)	4.90 (2.80)	1.28	0.79-1.76
	Tanum 2001	5.50 (3.20)	4.60 (4.40)	0.23	-0.47-0.92
	Baker	11.12 (5.48)	7.70 (5.30)	0.63	0.21-1.04
	Bennett	1.40 (0.32)	1.60 (0.20)	-0.74	-1.11-(-0.38)
	Haug 1994	5.40 (3.20)	1.40 (1.60)	1.50	0.77-2.23
	Haug 1995	4.30 (2.80)	1.80 (1.90)	1.04	0.75-1.34
	Kok	10.91 (4.42)	10.43 (4.08)	0.11	-0.47-0.69)
	Talley 1998	5.00 (3.40)	4.60 (3.00)	0.13	-0.17-0.42
	Talley 1998	4.40 (3.00)	3.10 (2.80)	0.46	0.08-0.84
	Pooled			**0.50**	**0.11-0.90**

Figure 2. OR of having anxiety

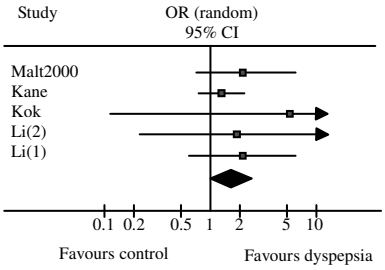


Figure 3. OR of having depression

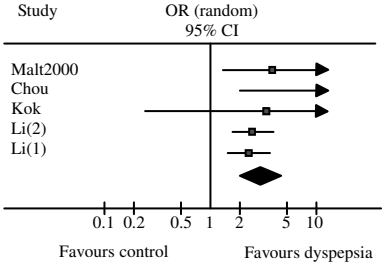


Figure 4. OR of having any psychiatric disease

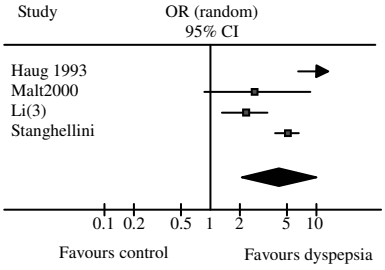


Figure 5. OR of having at least one life event

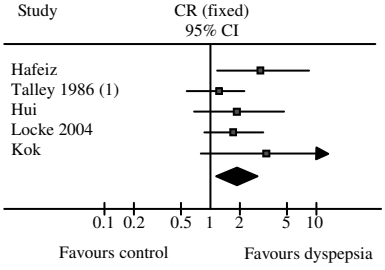


Figure 6. The SMD in depression scores

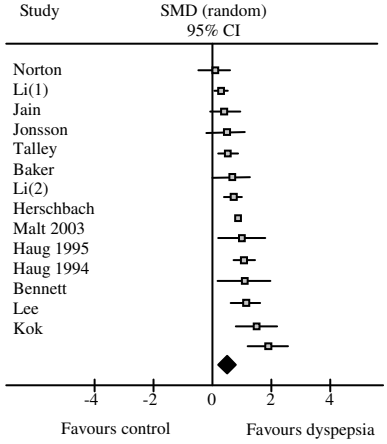


Figure 7. The SMD of (state) anxiety scores

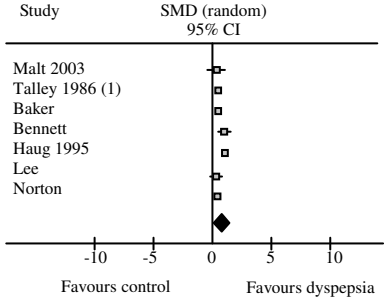


Figure 8. The difference in trait anxiety scores

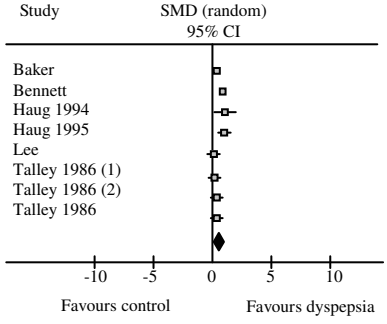


Figure 9. The difference in mean somatisation scores

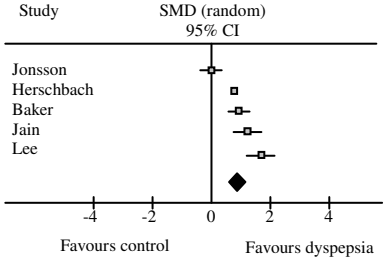
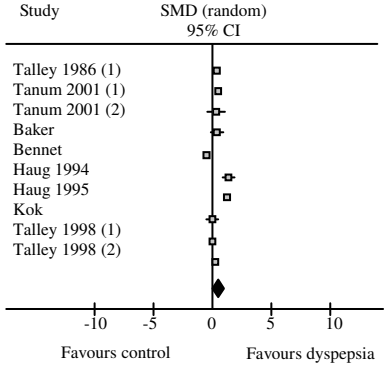


Figure 10: The difference in mean neuroticism scores



Major life events

Major life events were analysed in five studies (43, 45, 49, 51, 56) with 334 patients (Figure 5 and table 2). Four out of five studies reported no significant difference in the number of events between patients and controls. However, pooled results demonstrated significant difference between controls and dyspepsia patients without evidence for heterogeneity (p=0.57). The odds ratio for having one event in the dyspeptic group was 1.94 (95% CI 1.27 to 2.96) compared to the control group.

Personality traits

Fifteen studies reported data on the relation between dyspepsia and personality traits. The most frequently measured traits were: anxious personality (14, 25, 27, 35,

41, 56, 58), neuroticism (14, 25, 27, 41, 49, 56, 59, 60), extroversion (25, 35, 49, 56, 60), and somatisation (35, 41, 44, 46, 47). Again the results were heterogeneous ($p<0.1$), but the pattern is similar for all studies (Figure 8 and 9 and table 2). We found a medium effect for anxiety (SMD 0.51. 95%CI 0.28-0.74) and a large effect for somatisation (SMD 0.82. 95% CI 0.48-1.26).
From the personality traits extroversion and neuroticism, only for neuroticism a medium effect is found (SMD 0.50 95% CI: 0.11-0.90); no difference is found in extroversion between dyspepsia patients and controls (Figure 10 and table 2).

Coping style
We identified three studies measuring coping style (25, 28, 35). The questionnaires used were: Defence Style Questionnaire, Coping Flexibility Interview Schedule and Ways of Coping Checklist. It was not possible to combine results of these studies, because they all measured outcome differently, However, all studies confirmed that dyspeptic patients use a less adequate coping style than healthy controls. The study of Cheng et al (28) found that FD patients use more "direct-action" strategies and fewer "divert attention", "acceptance", "social support", and "relaxation" strategies to handle stressful life events. Dyspeptic patients prefer more action-oriented coping strategies when they encountered stressful life events. The use of action-oriented strategy in every situation would not always be applicable according to Cheng et al; for instance, when the stressful situation is not controllable. Bennett et al (25) found that FD patients use less effective coping skills, namely, neurotic and immature defences. Lee et al (33) showed that FD patients had significantly lower problem-focused coping and lower seeking of social support compared with healthy controls.

Discussion

The combined data from several studies show an increased presence of psychiatric and personality disturbances in patients with dyspepsia. Moreover, it demonstrates marked differences in frequency of major life events and coping behaviour between dyspeptic patients and healthy controls. To appreciate these results, some aspects of the present analyses need to be discussed.

Firstly, the numbers of published studies addressing these topics and in particularly case-control studies were below expectations. The reported outcome measures in the majority of these studies were means of psychometrically (self reported) measured

personality and psychiatric disorders. Only a limited number of studies actually classified dyspeptic patients as having a personality or psychiatric disorder or not. The latter studies showed homogeneous results in contrast to studies who reported arithmetical means of used questionnaires. Results from the studies presenting this kind of the results were very heterogeneous. Several explanations for the heterogeneity we found may be given (31). First, heterogeneity within the study populations. Several studies gave poor descriptions of how the patients and controls were included, or used different procedures for cases and controls. Second, potential confounders such as gender, education level, and socio-economic status were not consistently taken into account in the analyses of the data or appropriately matched in the design by the authors of the original publications. Third, we included studies that did not distinguish between dyspeptic and IBS symptoms and used these as one group (patients with functional gastrointestinal diseases). The justification for including the latter studies is their overlapping symptomatology. Over 50% of IBS patients also have dyspeptic symptoms (36, 37). Although heterogeneity between study results means that the study results are very different (e.g. they are testing a different hypotheses) we still decided to pool data. According to Harris and Rosenthal: "heterogeneity is analogous to individual differences among subjects within single studies and is common whenever many studies by different investigators using different methods are examined" (61). This is clearly the case in this meta-analysis.
Moreover, the variation between study results could also be "due to differences in the rate of occurrence of disease in the fraction of the population that is not exposed to the factor of interest rather than bias" (62). Indeed, the prevalence of different personality and psychiatric disorders vary between different populations as well as the prevalence of dyspeptic symptoms does. So, heterogeneity was expected from the beginning among these studies. The purpose of this meta-analysis was not to determine one "true" effect for the whole sample but rather to generate the highest possible certainty on the direction of the summarized effect of several psychosocial conditions in relation to dyspepsia (do dyspeptic patients score higher psychometrically or not) from samples with a various origin.

The results from studies with binary data showed that dyspeptic patients have an increased risk of having a psychiatric disorder, particularly depression. These results are supported by studies with continuous data that showed a very consistent pattern in distribution of the results. The distribution of the mean depression score is

medium to large meaning that dyspeptic patients score on average 0.5 to just above 0.8 SDU higher as compared to controls. Studies that measure anxiety, both trait and state, showed on average a medium effect. Direction of the distribution of anxiety scores shows that dyspeptic patients score 0.28 SDU to 0.88 SDU higher on anxiety scales than controls.

Major life events were significantly more common in the recent history of dyspeptic patients compared to healthy people. Studies included in this review reported that dyspeptic patients have especially more negative events. Patients classified the impact of events as more threatening compared with the reaction of healthy controls (25). Accordingly dyspeptic patients respond negatively to certain life events which could reflect their personality and coping strategies.

From studies on coping ability of dyspepsia patients (25, 28, 35) it can be concluded that they not prefer only one coping style, but rather use different coping styles. Active coping has been considered as more "healthy" in dealing with problems, yet not always applicable. For example, family and work related problems which are generally controllable could be solved using active coping. Dealing with health issues, emotion-focused strategies such as avoidance or seeking support are thought to be more appropriate (63). There is no agreement which coping strategy is the best. Coping strategies should be investigated in the light of treatment success or failure rather than comparing dyspeptic patients with healthy controls. Only than conclusions can be made about which coping strategies are more beneficial and which are not.

The exact quantitative causal effect of personality and psychiatric factors on the aetiology of dyspepsia cannot be derived from this analysis. The main reason for this is relatively poor quality of the studies which does not allow a firm conclusion over their results. On the other hand, these studies are the best evidence for investigating the association between dyspepsia and personality and psychiatric factors we have at this moment in this area. Although they have different quality, they were all very consistent in their results, namely showing that dyspeptic patients do have more depressive, anxious and somatic symptoms as compared to healthy controls.
Based on this, the personality and psychiatric factors should be considered in management of (functional) dyspepsia. This could be especially meaningful for

patients with recurrent symptoms who are not responding to known medical treatments (39, 40).

In conclusion, the summarized results of the available evidence in published studies support the view that personality, psychosocial and psychiatric problems play a role in dyspeptic symptoms. Since many studies and guidelines regarding dyspepsia currently focus on H pylori or adequate acid reduction our conclusion might revitalize older clinical hypothesis that upper abdominal symptoms at least have a multiconditional aetiology. More population based, well designed prognostic studies addressing psychological factors as well as different treatment strategies for dyspepsia are needed to be able to draw more detailed conclusions that might help the clinician in how to make use of this knowledge.

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Chapter 3

Psychopathology is associated with dyspeptic symptom severity in primary care patients with a new episode of dyspepsia

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Abstract

Objective: To study the association between dyspeptic symptom severity and psychopathology, major life events and coping ability in patients with a new episode of dyspepsia.

Design: Cross-sectional study in primary care.

Setting: 127 general practices in the Netherlands.

Patients: 664 patients with a new episode of uninvestigated dyspepsia, aged >18 years.

Measurements: Dyspeptic symptom severity was measured using the validated 8 symptom Veldhuyzen van Zanten questionnaire. Psychopathology was measured using the Symptom Check List-90 (SCL 90). Major life events were measured with a modified version of the Social Readjustment Rating Scale (SRRS). Coping styles were measured by a short version of the Utrecht Coping Questionnaire, distinguishing six coping styles. Linear regression was used to assess the relationship between dyspepsia symptom severity and psychological factors.

Results: Dyspeptic symptom severity was positively correlated with the presence of depression ($p<0.01$), somatisation symptoms ($p<0.01$), use of an active coping style ($p<0.01$) and negatively correlated with age ($p<0.01$).

Conclusion: Primary care patients consulting with dyspepsia have higher levels of depression and somatisation especially at younger age. An Active coping style is associated with dyspepsia symptom severity.

Introduction

Dyspepsia is traditionally defined as "upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptoms considered to originate form the upper abdominal tract" (1). Although dyspepsia is not a life threatening condition, it represents a significant health problem with substantial negative impact on quality of life and health care consumption (2-4).

Psychological factors such as psychiatric illness and personality disorders have been considered to play a role in the development of dyspeptic symptoms (5-7). Indeed, several clinical studies have reported higher depression and anxiety rates in dyspeptic patients (8-10). These patients frequently show higher levels of neuroticism, psychological distress and somatisation as compared to non-dyspeptics (11,12). More over, population studies reported that individuals with dyspeptic symptoms have more overall psychiatric co-morbidity compared to the healthy population (13,14).

Stressfull life events in the patients' social environment are also thought to be associated with the onset or exacerbation of dyspeptic symptoms (15). Recent studies showed that there is an association between functional gastrointestinal disorders (FGID) and life threatening events (16). Moreover, chronic stress seems to be a strong predictor of symptom intensity and clinical outcome of patients with FGID (17).

The relation between dyspepsia and psychosocial factors is most intensively studied in patients with endoscopically confirmed functional dyspepsia, mostly in secondary and tertiary care settings. Though, the majority of dyspeptic patients seeking medical attention are managed in primary care. Patients referred to secondary care are known to have more severe dyspeptic symptoms and symptoms of psychological disturbances (18, 19). For this reason results from secondary care studies suggesting an association between psychological factors and dyspepsia cannot automatically be applied to the primary care population. More detailed research is required to understand the association between dyspeptic symptom severity and symptoms of psychopathology in the broader patient population. The aim of this study was to investigate the relation between dyspeptic symptom severity and psychological and psychiatric morbidity in a primary care population consulting with a new episode of dyspepsia.

Methods

Design

This is a cross-sectional analysis of baseline data from all patients enrolled in the Dutch study of InitiAl Management Of Newly diagnosed Dyspepsia (DIAMOND). This is a large multicenter randomised clinical trial comparing two different treatment strategies with antacid drugs in primary care patients consulting with dyspepsia. The DIAMOND study design has been described in detail elsewhere.(20)The study has been approved by the Medical Ethics Committee of the University Medical Centres Utrecht, Maastricht and Nijmegen.

Recruitment

Between October 2003 and December 2006, patients presenting with dyspepsia were recruited at 127 primary care centres in the southern and central part of the Netherlands. Patients were found eligible for the study if they had a (new) episode of dyspepsia, were 18 years or older and were able to fill out the Dutch questionnaires.

Patients were excluded if they used prescribed acid suppressive medication in the three months prior to consultation, had upper GI endoscopy in the year before inclusion, were diagnosed with malignancy of GI tract, had a contraindication to the study medication, were pregnant or had alarm symptoms (e.g. weight loss, bleeding or disturbed food passage). Before starting with the trial patients received the trial information folder and they gave written informed consent.

Measurements

Gastrointestinal Symptoms

Dyspeptic symptoms were classified with a dyspepsia symptom questionnaire, validated by Veldhuyzen van Zanten (21). It covers eight essential dyspeptic symptoms: epigastric pain, burping/ belching, heartburn, bloating, flatulence, sour taste, nausea and halitosis. We extended the registration of the symptom severity to a 7 point Likert scale graded: (0) none, (1) minimal, (2) mild, (3) moderate, (4) moderately severe, (5) severe, (6) very severe. The symptom severity score is calculated by the sum of all items (range 0-48). Higher scores indicate higher severity. Patients were classified as having mild, moderate and severe symptoms based on tertiles in the mean symptom score.

Psychopathology

Psychopathology was measured using the Dutch version of the Symptom Check List-90 (SCL 90), which is a self-reporting, validated instrument with 90 questions, measuring 9 dimensions of psychological distress and psychopathology on a 5 point Likert scale (22). These dimensions are: anxiety (representing anxiety symptoms and disorders), agoraphobia (representing fear of public spaces, crowds an leaving home), depression (persistent mood disturbance, feelings of hopelessness, guilt, worthlessness, helplessness, loss of interest or pleasure in sex, and decreased energy), somatisation (marked by multiple medically unexplained complaints, such as chronic pain and fatigue), obsessive-compulsive disorder (characterized by recurrent thoughts, feelings, ideas or sensations (obsessions) by behaviours which are experienced as compulsive), interpersonal sensitivity (reflecting feelings of uneasiness and marked discomfort when interacting with others, as well as feelings of personal inadequacy and inferiority). hostility (representing feelings, thoughts and behaviours which characterise negative mood and anger), sleeping disturbances (symptoms of early awakening, restless sleep and difficulties with falling asleep). The dimension psycho-neuroticism represents the overall level of psychic and bodily dysfunction. The SCL 90 scores of our dyspeptic patient population were compared with the mean SCL 90 scores from a Dutch general population sample, which is provided by the user manual (22).

Major Life Events

We used a modified version of Social Readjustment Rating Scale (SRRS) developed by Holmes and Rahe in 1967, comprising 38 life events listed from most stressful to less stressful. The original scale is made for and validated in the US population. We subcategorised the first 19 items as “highly stressful” events and items 20-38 as “stressful” events.

Coping style

Coping styles were measured by a short version of the Utrecht Coping Questionnaire consisting of 17 items (23). Six coping styles are distinguished, classified as: active coping (solving the problem step-by-step, thinking it over before acting, applying goal-directed behaviour), seeking support (seeking comfort and understanding by others), avoidance coping (waiting for things to happen, avoiding the problem), palliative coping (seeking distraction, keeping yourself occupied in order not to think of problems), religious coping (pray, thinking that the situation is unavoidable,

because it is a work of higher powers) and passive reaction (acceptance of the situation). Coping styles were rated on a four-point Likert scale ranging from (1) seldom or never, (2) sometimes, (3) often and (4) very often. Scale scores are the sums of the individual items. Higher scores indicate that the specific coping style is more often adopted.

Demographic data

A self-administered postal questionnaire was used for assessment of patient's age (years), gender, height (m), weight (kg), marital status, level of education, working situation, as well as life style factors (consumption of alcohol, coffee, and smoking status). The GP recorded any history of psychiatric disorders within 5 years prior to inclusion as well as any current psychiatric disorders. Marital status was classified as living together (married, partnership) or being single (unmarried, widowed or divorced). Level of education was recorded according to highest level completed (0=no education; 7= academic level). The working situation was classified as employed (paid job, owns business) or unemployed. Alcohol consumption, coffee consumption and smoking status were recorded as current users (yes/no). Body mass index (BMI) was calculated from self reported weight and height kg/(m²). Overweight was defined as BMI>25.

Data analysis and statistics

Data were analysed with SPSS for Windows, version 14.0. Means and standard deviations (SD) were computed for continuous variables and medians and inter quartile range (IQ range) for continuous variables with skewed distribution. To test differences in socio-demographic factors between dyspepsia subgroups parametric and non-parametric statistical tests were used when appropriate (ANOVA, Kruskal-Wallis and X^2-test).

To retain power and precision as well as to prevent bias from missing values in a selective group of patients a single imputation procedure in SPSS version 14.0 was used. We imputed missing values (due to full or partially non response) for a range of 4%-15% of the questions of the SCL-90, gastrointestinal symptom questionnaire, UCL and MLE.

A multiple linear regression model was used to examine the independent relation between psychological and socio-demographic factors and upper GI symptom severity, with the sum of the dyspepsia score as dependent variable. Adjustments were made for age and gender. All variables that were univariately associated (p□

0.1) with symptom severity or were biologically plausible were included in the analysis.

SCL-90 subscales were dichotomised at the 65th percentile according to the "normal" reference population scores (mean score plus standard error).

Results

Patients

A total of 664 patients were included in the DIAMOND study. Slightly more women (54.2%) than men participated in the study (table 1).

The mean age of all patients was 47.4 (SD=14.2) years 54.6% of the patients were overweight (BMI >25). Almost 9 percent of the patients were actively treated for psychiatric disease at the time of inclusion.

Of all patients included 187 (33.4%) had mild dyspeptic symptoms, 190 moderate (33%) and 167 severe (32.7%) (Table 1).

Patients with severe dyspepsia were younger, and more likely to have psychiatric diagnoses in past 5 years ($p<0.01$). Patients with mild complaints were older, had a lower level of education and a higher frequency of unemployment ($p<0.05$) as compared to the other patient groups. Patients with moderate dyspepsia had a higher frequency of overweight (61%; $p<0.05$, Table 1).

Psychological factors and dyspeptic symptom severity

Except for agoraphobia, dyspeptic patients had a significantly higher score on all SCL-90 dimensions (all $p<0.01$) as compared to the general population. The mean scores (sd) for the general Dutch population were: agoraphobia 7.86 (2.34); anxiety 12.76 (4.41); depression 21.58 (7.56); somatisation 16.68 (5.34); interpersonal sensitivity 12.63 (4.25); obssesive-compulsive disorder 24.05 (7.64); hostility 7.22 (2.10); sleeping disturbances 4.46 (2.20); and psycho neuroticism 118.28 (32.38).

Patients with severe dyspeptic complaints had higher scores on all SCL-90 dimensions as compared to mild and moderate dyspeptic patients ($p< 0.01$) (Table 2). The psycho-psychiatric profile of patients with mild dyspeptic symptoms did not differ from the general population.

Highly stressful life events were more often reported by patients with severe dyspeptic symptoms ($p< 0.05$) (Table 3). These patients also adopted more active, avoidance, and support seeking coping styles (all $p< 0.05$) as compared to other patients (Table 4).

Table 1: Baseline patient characteristics

	All	SD	Mild dyspepsia	SD	Moderate dyspepsia	SD	Severe dyspepsia	SD	P-value
Nr. of patients	664		218 (32.8%)		230 (34.6%)		216 (32.5%)		
Age mean (sd)	47.1	14.6	50.8	15.4	46.7	14.2	43.7	13.2	<0.05
Mean symptom score (sd)	16.8	6.5	9.6	2.9	16.7	1.7	24.1	3.8	
BMI mean (sd)									
BMI<=25 (%)	26	4.0	25.8	3.6	26.5	4.2	25.8	4.3	NS
BMI >25 (%)	45.3		50		39		48		
Gender	54.7		50		61		52		<0.05
Male (%)	45.8		44.5		51.3		41.2		
Female (%)	54.2		55.5		48.7		58.8		NS
Marital tatus									
Living together (%)	75.6		72.5		78.8		75.5		NS
Single (%)	24.4		27.5		21.3		24.5		
Education (0=no; 7=academic)	3.6	1.8	3.4	1.8	3.8	1.8	3.7	1.8	<0.05
Working situation									
Employed (%)	62.6		55.5		69.1		61.6		<0.05
Unemployed (%)	37.8		44.5		30.9		38.4		
Alcohol intake									
Yes (%)	73.2		69.3		75.2		75		NS
No (%)	26.8		30.7		24.8		25		
Coffee intake									
Yes (%)	87.8		88.5		87.4		87.5		NS
No (%)	12.2		11.5		12.6		12.5		
Smoking status									
Yes (%)	27.7		23.9		27.8		31.5		NS
No (%)	72.3		76.1		72.2		68.5		
Psych. Diag. <5 y									
Yes (%)	20		17		17		26.4		<0.05
No (%)	80		83		83		73.6		
Current psych. diag.									
Yes (%)	10		7		10		12		NS
No (%)	90		93		90		88		

Psych. Diag. <5 y= Psychiatric diagnoses 5 years prior to inclusion; Current psych. diag.= Current psychiatric diagnoses.

Table 2: Mean scores and differences between dyspepsia subgroups on 9 dimensions of SCL-90.

		Mild dyspepsia (N=218)		Moderate dyspepsia (n=230)		Severe dyspepsia (n=216)		a	b
	Range	Mean	sd	Mean	sd	Mean	sd		
AGO	7-35	7.6	1.46	8	2.2	8.4	2.70	*	*
ANX	10-50	12.3	2.80	14	4.38	15.7	6.1	**	**
DEP	16-80	21	5.5	24.4	8.5	27.5	10.6	**	**
SOM	12-60	18.2	4.3	21.3	6.7	24.8	7.2	**	**
IN	9-45	12.4	3.7	14.5	5.5	16	6.1	**	**
SEN	18-90	22	6.2	24.7	9.13	27.5	11	**	**
HOS	6-30	6.8	1.35	7.7	2.4	8.4	2.9	**	**
SLEEP	3-15	4.8	2.2	5.9	2.9	6.1	3.1	**	ns
PSYCHO NEUR	90-450	113.6	22.4	133.5	37.5	145.9	43.3	**	**

a= difference between Mild and Moderate+Severe dyspepsia groups; b= difference between Severe and Moderate+Mild dyspepsia groups; *significant at p< 0.05; ** significant at p<0.01; ns=not significant

Table 3: Mean scores (sd) on Utrecht Coping List and median scores (IQ range) on the Life Events list in the three dyspepsia subgroups.

	Range	Mild dyspepsia (N=218)		Moderate dyspepsia (n=230)		Severe dyspepsia (n=216)	
Life events median (IQ range)			sd		sd		sd
Highly stressful †		1		1		1	
(IQ range)		(0-1)		(0-2)		(1-2)	
Stressful		1		2		2	
(IQ range)		(1-2)		(1-3)		(1-3)	
Patients with >=1 highly stressful events (%)		66.5		71.3		79.6	
Patients with >=1stressful events (%)		76.1		81.3		79.6	
UCL mean (sd)							
Avoidance coping‡							
	2-8	3.4	1.0	3.8	1.2	3.8	1.3
Active coping †	5-20	13.4	3.0	13.1	3.0	13.9	2.9
Palliative coping	2-8	4.4	1.2	4.4	1.3	4.6	1.2
Seeking support†	5-20	11	3.3	11	3.1	11.6	3.2
Passive reaction	1-4	1.9	0.7	2.1	0.7	2.0	0.7
Religious coping	2-8	3.0	1.2	3.1	1.2	3.2	1.2

†significantly different between severe group and mild/moderate group; ‡ significantly different mild/moderate and mild/severe group;

In multivariate analysis younger age ($p<0.05$), the presence of an active coping style ($p<0.01$), somatisation ($p<0.01$), and depression ($p<0.01$) were found to be independently associated with dyspeptic symptom severity (Table 4). All predictors were positively associated with symptom severity, only age was negatively associated. In total these factors explain about 25 % of the variance in the dyspeptic symptom score.

Table 4: Linear regression model, relating the severity of dyspeptic symptom score with patient characteristics and psychosocial factors.

Coefficients	B	Se	Beta	t	Sig.	95%CI for B	
(Constant)	5.23	1.68		3.12	<0.01	1.93	8.53
Age	-0.07	0.02	-0.14	-4.03	<0.01	-0.10	-0.03
Depression	0.08	0.03	0.11	2.76	0.01	0.02	0.14
Somatisation	0.36	0.04	0.38	9.53	<0.01	0.29	0.44
Active coping style	0.26	0.08	0.11	3.17	<0.01	0.10	0.41
Education	0.25	0.13	0.07	1.95	0.05	0.001	0.51
BMI	0.85	0.45	0.07	1.87	0.06	-0.04	1.74

Adjusted for: age, gender, education level, employment status

Discussion

The aim of this study was to explore the relation between dyspepsia symptom severity and psychopathology, major life events and coping ability in primary care patients with a new episode of dyspepsia.

We found a “dose-response” relationship between dyspeptic symptom severity and psychopathology and coping style. In particular the presence of somatisation, depression, younger age and the use of an active coping style were found to be associated with severe dyspepsia.

The psychological profile of patients with mild dyspepsia does not differ from the general population In contrast, patients with moderate and severe dyspepsia score higher than the average population on all dimensions of SCL90. These results did not alter when the patients with a historical or current psychiatric diagnosis were excluded from the comparison. In many patients symptoms of psychiatric illness and or psychosocial problems coincide with gastrointestinal disturbances (5,6,24,11)Our results confirm this relationship and add evidence that there is a gradual transition from mild to severe psychosocial morbidity parallel with dyspepsia symptom severity.

In a line with previous studies (5,6,11,27) we confirmed that somatisation is strongly associated with dyspeptic symptom intensity. This association could be explained by the fact that this SCL-90 dimension includes two items, which in some cases could be reflexion of upper gastro-intestinal complaints ("noxious feeling in the stomach" and "chest pain"). However, in additional analysis in which we removed these items from SCL-90, somatisation still had the highest correlation with dyspepsia symptom severity, indicating that these patients generally have more bodily symptoms, not biased by the presence of the GI symptom questions.

Highly stressful life events were only univariately associated with severe dyspeptic symptoms. An explanation for this finding could be that stressful events do not directly influence symptom perception, but have an indirect effect through personality and coping style. Earlier studies reported inconsistent results regarding this association. For example, Basely et al found that only negative life events have significant impact on physical and psychological symptoms. Bennett et al found that chronic life problems can influence clinical outcome of patients with FGID.(17) In contrast, Locke et al reported that life threatening events are associated with IBS but not with non-ulcer dyspepsia.(16) Talley did not identify any association between major life events and the course of dyspepsia.(28,29)

Coping strategies that dyspeptic patients use to deal with stressful situations vary with symptom intensity. When examining differences in the use of coping styles, it is notable that patients with mild dyspepsia are less likely to use less an avoidance coping style, while those with severe dyspepsia use significantly more active, avoidance, and support seeking coping strategies.. In multivariate analysis only the use of an active coping style was strongly associated with dyspepsia symptom severity. Active coping, is a problem-focused strategy which is usually applied in situations where stressors are controllable, like in f.i. work- or family- related problems. Results from studies (30,31) on coping ability of dyspepsia patients so far did not provide consistent conclusions. Cheng et al found that dyspeptic patients use more active coping styles while Lee et al found that these patients use less problem focused strategies. Studies in patients with different chronic diseases (32-34) have shown that the use of an active coping style is generally associated with a better prognosis and treatment outcome.

Our cross sectional study design had some limitations. All measurements were done at one point in time, which does not allow any conclusion about causality. Major life events were also measured retrospectively; recall bias resulting in under and over

reporting may have affected the results. As consultation is one of the control mechanisms the predominance of an active style in our sample may partly be due to inclusion bias.

Psychological state was assessed using a self-administered questionnaire. Therefore the results are a subjective perception of the patient's complaints. It is possible that in some cases (f.i. somatic complaints) symptoms were exaggerated or underreported due to denial (22).

In conclusion, symptoms of depression and somatisation are associated with dyspepsia symptom severity in patients consulting with new episode of dyspepsia

General practitioners and gastroenterologists should be aware of possible underling psychological problems in their management of patients with moderate and severe dyspepsia, especially in younger patients. In addition to drug treatment, routine exploration of the psychopathological background of the patient should be recommended in the daily management of severe dyspepsia.

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Chapter 4

CYP2C19*2 polymorphism does affect PPI treatment success in dyspepsia

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Abstract

Background: Proton pump inhibitors (PPI) are commonly used drugs in the treatment of dyspepsia in primary care. Effectiveness is found for about 40% of the patients with uninvestigated dyspepsia. PPI's are metabolized by the liver enzyme CYP2C19. The activity of CYP2C19 is influenced by genetic polymorphisms, reflected in rapid, intermediate and poor PPI metabolising patients.

Aim: We studied the effect of CYP2C19 genotype status on the clinical outcome of 4 weeks PPI treatment compared with psychological problems and demographic factors in uninvestigated dyspepsia.

Methods: Data were analysed from 323 patients participating in a multicenter randomised trial with 4 weeks PPI treatment for dyspepsia. Treatment success was defined as adequate symptom relief after 4 weeks, not requiring a next treatment step. According to their CYP2C19*2 genotype patients were classified as rapid metabolizers (RM, wt/wt), intermediate metabolizers (IM, wt/*2) and poor metabolizers (PM, *2/*2).

Dyspeptic symptoms were registered with a validated questionnaire, measured before, after 2 weeks and after 4 weeks of treatment. H. pylori status was determined by measuring IgG antibodies in serum.

Differences between the three genotype groups were evaluated using the chi-square test, Fisher's exact test and one way ANOVA. Univariate and multivariate logistic regression analysis was used to assess determinants of PPI treatment success.

Results: The distribution of CYP2C19 genotype among the participating patients was: 71% RM. 25.6% IM and 3.4% PM. Treatment was successful in 70% of PM. 58.7% of IM and in 55.3 % of RM ($p > 0.05$). Symptom improvement, measured as the percentage of decrease in mean initial symptom score after 4 weeks, was 65.8% in PM. 48.7 % in IM group and 44.3% in RM group (trend test $p=0.02$). In multivariate analysis PPI treatment outcome at 4 weeks was only independently associated with baseline dyspeptic symptom severity (OR 0.94 95%CI:0.90-0.97).

Conclusions: Symptom reduction after 4 weeks of PPI treatment was higher among poor metabolizers. However, the clinical relevance of differences in treatment success due to CYP2C19*2 genotype remains to be determined. Severe dyspeptic symptoms are associated with poor treatment outcome.

Introduction

Dyspepsia is a common condition in the population. It is defined as the presence of symptoms thought to originate in the upper gastrointestinal tract including any of the following symptoms: epigastric burning, epigastric pain, postprandial fullness and early satiation. (1) The general population prevalence ranges from 25-40% worldwide (2) The prevalence of patients consulting for dyspepsia in primary care ranges from 3% to 8%(3-5).
Proton pump inhibitors (PPI's) are frequently used in the pharmacotherapy of dyspepsia, consuming up to 10% of the total national pharmacology budget. They have proven effectiveness for esophagitis, gastro-esophageal reflux disease (GERD), and peptic and duodenal ulcer disease, with healing rates ranging from 50% to 90% (6-10). However, in patients with less differentiated or uninvestigated dyspepsia, often occurring in primary care, complete relief of symptoms is only seen in about 40% of the patients (11;12). The ability to predict variability in PPI response and to individualize PPI dosage will result in a better outcome of PPI treatment, thus reducing the health care costs. Also, identification of factors associated with success or failure of PPI treatment might contribute to a more cost-effective treatment of acid related disorders.

The enzyme cytochrome P450 CYP2C19 (13-16) plays an important role in the metabolization of PPI's. It is responsible for the inactivation of acid suppressing effect of PPI's. Several variant alleles can lead to inactivity of this enzyme. This is reflected in phenotypes with poor (PM), intermediate (IM) and rapid metabolisation (RM). Among Caucasians CYP2C19*2 allelic variant is the main homozygous PM genotype.

Due to differences in enzyme activity, it is conceivable that the CYP2C19 genotype status will influence the efficacy of PPI therapy. In RM, intragastric pH levels and plasma drug concentration are demonstrated to be significantly lower than in PM and IM after administration of a single dose of omeprazole 20 mg or lansoprazole 30 mg (20;21). Compared to individuals with the PM and IM, the RM phenotype shows significant lower cure rates of GERD, esophagitis(22), peptic/duodenal ulcers, and Helicobacter pylori eradication(23;24).

Apart from CYP2C19 polymorphisms, several other factors can influence the outcome of PPI treatment in dyspepsia. These factors include age, gender(21), H. pylori infection(22) and co- medication(17;24-26)
We examined the effect of the CYP2C19 genotype on the effectiveness of PPI treatment in patients with dyspepsia.

Methods

Study design
This analysis is part of the DIAMOND study, a prospective, multicenter, randomized trial performed in 127 primary care practices comparing the effectiveness of two treatment strategies for uninvestigated dyspepsia: step-up (antacid-H2RA-PPI) versus step-down (PPI-H2RA-antacid). Details of the study are described elsewhere (53). In the current study we analysed data from the patients who were randomly assigned to the step-down treatment arm. They were treated with a single dose of pantoprazol 40 mg for one month as initial treatment medication (figure1).
Patients
Inclusion of patients was started after approval of the DIAMOND study protocol by the medical ethics committee (METC) of the University Medical Centre (UMC) Utrecht and the UMC St. Radboud, Nijmegen. Patients of 18 years and older presenting with dyspepsia were included. Dyspepsia was defined as episodic or persistent symptoms including abdominal pain or discomfort, referable to the upper gastrointestinal tract (including reflux symptoms).
Patients were excluded if they were prescribed acid suppressive medication in the three months prior to consultation, had upper GI endoscopy or H.pylori eradication in the year before inclusion, were diagnosed with malignancy of GI tract, had contra-indication to the study medication, were pregnant, had alarm symptoms (e.g. weight loss, bleeding and disturbed food passage), or had insufficient knowledge of the Dutch language.
Outcome
Treatment success was defined as adequate symptom relief after four weeks of PPI treatment without further requirement of medication.
Data collection
Demographic data (age, gender, ethnicity, co-medication use) were obtained at baseline. Dyspeptic symptom severity was measured by the Veldhuyzen van Zanten dyspepsia questionnaire, which is a validated symptom questionnaire (33) measuring

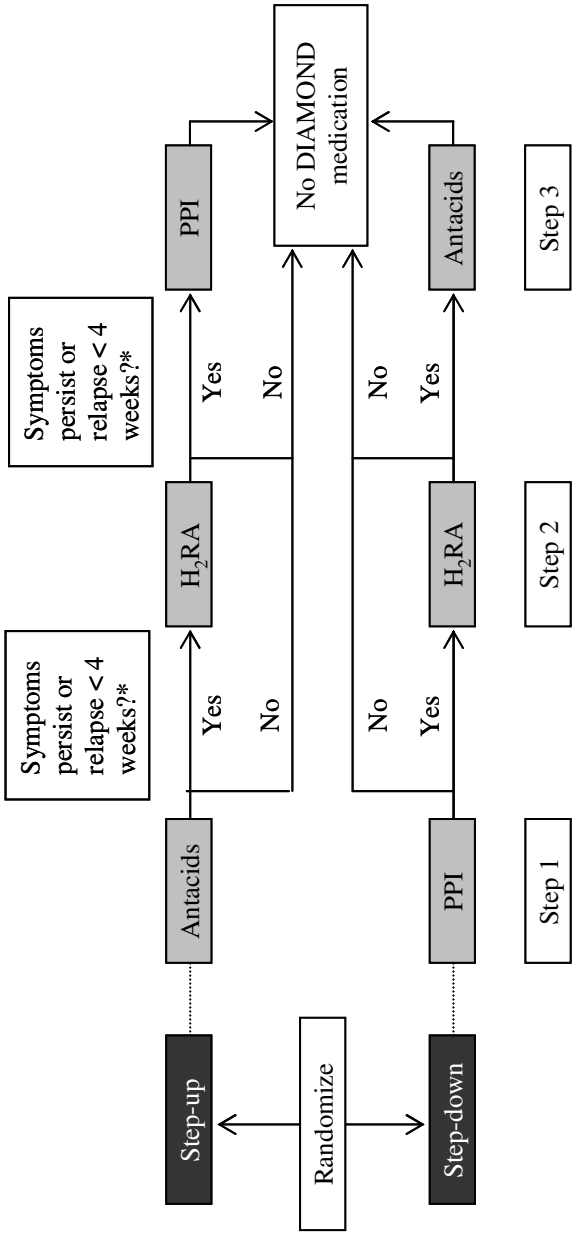


Figure 1. Treatment flow chart.

eight dyspeptic symptoms on a 7 point Likert scale. The sum score range from 0 to 48, with higher score indicating more severe complaints. Based on tertiles of the sum score distribution, patients were classified as having mild (score 0-13), moderate (14-19) or severe (20-max) dyspepsia. Symptoms were measured at baseline (first visit = T0), two weeks (T1) and 4 weeks after the start of the treatment (T2).

Two samples of venous blood were drawn. One sample was used to determine Helicobacter pylori antibodies (IgG) in serum (Pylori set EIA-G III; Orion Diagnostica Finland). A titer of more than > 20 units/ml was considered as a threshold for infection. The other sample was used for DNA extraction and determination of CYP2C19 genotype.

*Genotyping of CYP2C19*2 polymorphismn*

Genomic DNA was extracted from whole blood using the QIAamp DNA blood minikit (Qiagen, Hilden, Germany). Genotyping was performed by Molecular Beacon assay using the iCycler iQ real-time PCR detection system (BioRad, Hercules, CA, USA). The assay was carried out in a total volume of 25 µl, containing 50 ng of genomic DNA, 12.5 µl 2□ iQ Supermix (BioRad, Hercules, CA, USA), 500 nM of each primer, and 200 nM of each molecular beacon. MgCl2 was added to obtain a final concentration of 4 mM. The following primers were used:

5'-GAGCTTGGCATATTGTATCTATACC-3' (forward) and

5'-TACTTTCTCCAAAATATCACTTTCC-3' (reverse). Sequences of the Molecular Beacons were

5'-FAM-CGCGATTTATGGGTTCCCGGGAAATAATCATCGCG-DABCYL-3' (G-allele specific) and

5'-TXR-CGCGATTTATGGGTTCCTGGGAAATAATCATCGCG-DABCYL-3' (A-allele specific). The PCR thermal cycling protocol applied consisted of an initial denaturation and enzyme activation step of 95°C for 3 min, followed by 40 cycles of 95°C for 30 s, 60°C for 1 min and 72°C for 45 s. In each run representative samples from each genotype were inserted. To validate genotyping by the Molecular Beacon assay, polymerase chain reaction-based restriction fragment length polymorphism analysis was performed in a set of randomly chosen patients. For this purpose the polymerase chain reaction fragments were digested with SmaI overnight at 25°C and separated by 2.5% agarose gel electrophoresis. SmaI cuts the PCR product in two parts (107 and 64 bp). Concordance was 100%.

Data analysis

All statistical analyses were performed with SPSS for Windows, version 14.0

To retain power, to improve precision and to prevent bias from missing values (due to non-response) a single imputation procedure in SPSS version 14.0 was used, imputing missing values on the items of the gastrointestinal symptom questionnaire at baseline (on average 10%), after 2 weeks (on average 19%), after 4 weeks (on average 23%), medication use (10%) and other covariates (<4%) To avoid bias due to race related differences in genotype distribution we excluded non Caucasian patients from the analysis.

According to their genotype status patients were classified as rapid metaboliser (RM; wild type/wild type), intermediate metaboliser (IM; wild type/variant allele) and poor metabolisers (PM; variant allele/variant allele).

Differences between the three groups regarding demographic data, dyspepsia symptom severity and dyspeptic symptom reduction were assessed using chi-square test, Fisher's exact test (which was used when one of the genotypes had expected counts less than five) and one-way ANOVA. The chi-square test was used to analyse any significant difference in allele frequency between successfully and unsuccessfully treated patients.

To determine risk factors associated with treatment outcome, univariate and multivariate logistic regression analysis was performed. All factors univariately associated with treatment outcome at $p < 0.25$ as well as biologically plausible factors (age, gender, H. pylori titer >20, use of co-medication which is metabolised by CYP2C19) were included in a logistic regression model. OR's with 95% confidence intervals (95% CI) were calculated.

Results

Patients

From the 664 patients included in the DIAMOND study, 323 patients were randomised to the step-down arm, of whom 303 (94 %) were of Caucasian origin. Genotype was obtained from 293 patients (97%), from 10 (3%) patients no blood samples were available. From all genotyped patients, 166 (56.7%) were treated successfully with 4 weeks PPI treatment, in 127 patients (43.3 %) the PPI treatment failed.

The proportions of PM, IM and RM genotypes in the study population were 3.4%, 25.6% and 71.0% respectively. The frequency of the more common G allele was

84% and the frequency of the rare A allele was 16%. These frequencies were in Hardy –Weinberg equilibrium, and the distribution was in a line with reported frequencies for Caucasian populations [13].

Slightly more females (54.6%) than males were included and the mean age was 47.9 (SD 14.6) years. A Helicobacter pylori antibody titer of more than > 20 units/ml was observed in 33.4 % of the patients. No significant differences were found between the genotype groups regarding demographic data, symptom score, H. pylori IgG antibody titer and psychological co morbidity (table 1).

Table1: Baseline patient characteristics

	RM	IM	PM	Total
N (%)	208 (71)	75 (25.6)	10 (3.4)	293
Gender				
Female (%)	57.2	49.3	40	54.6
Age in years (mean,sd)	47.2 (14.7)	49.7 (13.9)	49.4 (16.8)	47.9 (14.6)
<= 45 years (%)	48.1	38.7	50.0	45.7
> 45 years (%)	51.9	61.3	50.0	54.3
H. pylori				
Negative (%)	65.7	66.7	8.0	45.7
Positive (%)	34.3	33.3	20.0	54.3
GI symp.score (max 48) (mean,sd)	16.7 (6.4)	16.4 (7.0)	15.2 (7.4)	16.5 (6.5)
0-13 (%)	31.3	32.0	40.0	31.7
14-19 (%)	36.5	34.7	30.0	35.8
20-max (%)	32.2	33.3	30.0	32.4
Co-medication				
Metabolisation by CYP2C19 (%)	11.1	12.0	10.0	11.3
Metabolisation other pathway (%)	88.9	88.0	90.0	88.7

Treatment outcome

Treatment success was observed in 55,3% of the patients in the RM group, 58,7% in the IM group and 70% in the PM group. Although in line with the hypothesis that PM could be associated with treatment success, this difference was not statistically significant (table 2).

The only factor associated univariately ($p< 0.25$) with a positive outcome of 4 weeks PPI treatment was dyspepsia symptom severity (OR 0.94 95%CI: 0.9-0.97). After adjustment for age and gender (table 2) in multivariate analysis symptom severity (OR 0.94; 95%CI: 0.9-0.99) remained independently associated with treatment outcome.

Changes in symptom score

Changes in mean dyspeptic symptom score were analysed between baseline and two weeks and between baseline and four weeks after the start of treatment. From the 293 patients who started, 9 (3%) patients proceeded to step 2 after only 1 week of PPI treatment. They were excluded from the comparison because one week was not considered as an adequate treatment period. Compared to the baseline symptom score the mean decrease in symptom score at 2 weeks was 36.5%, 34.1% and 31.6% in the RM, IM and PM group respectively (table 3). After four weeks of PPI treatment symptom reduction was 44.3% in the RM group, 48.7% in the IM group and 65.8 % in the PM group compared to baseline symptom score (table 3 and figure 2). The test for trend in symptom reduction from RM via IM to PM at 4 weeks however, was significant (p-value= 0.02).

Discussion

In this study CYP2C19 genotype status did affect the clinical outcome of PPI treatment, in the sense that we found a positive trend to increasing treatment success among poor metabolizers. However, dyspeptic symptom severity was the only factor independently associated with PPI treatment outcome.

Treatment success, defined as adequate symptom relief after 4 weeks of PPI treatment, was achieved for 56.7 % of the patients. 55.3% of the patients with RM phenotype were treated successfully and of the patients with IM phenotype 58.7% had a positive outcome. This is in line with previous studies which reported that on average 40%-60% of primary care patients benefit from PPI treatment (11, 12). However, a small group of patients with PM phenotype showed much better results.

Table 2: Summary of factors associated with treatment outcome

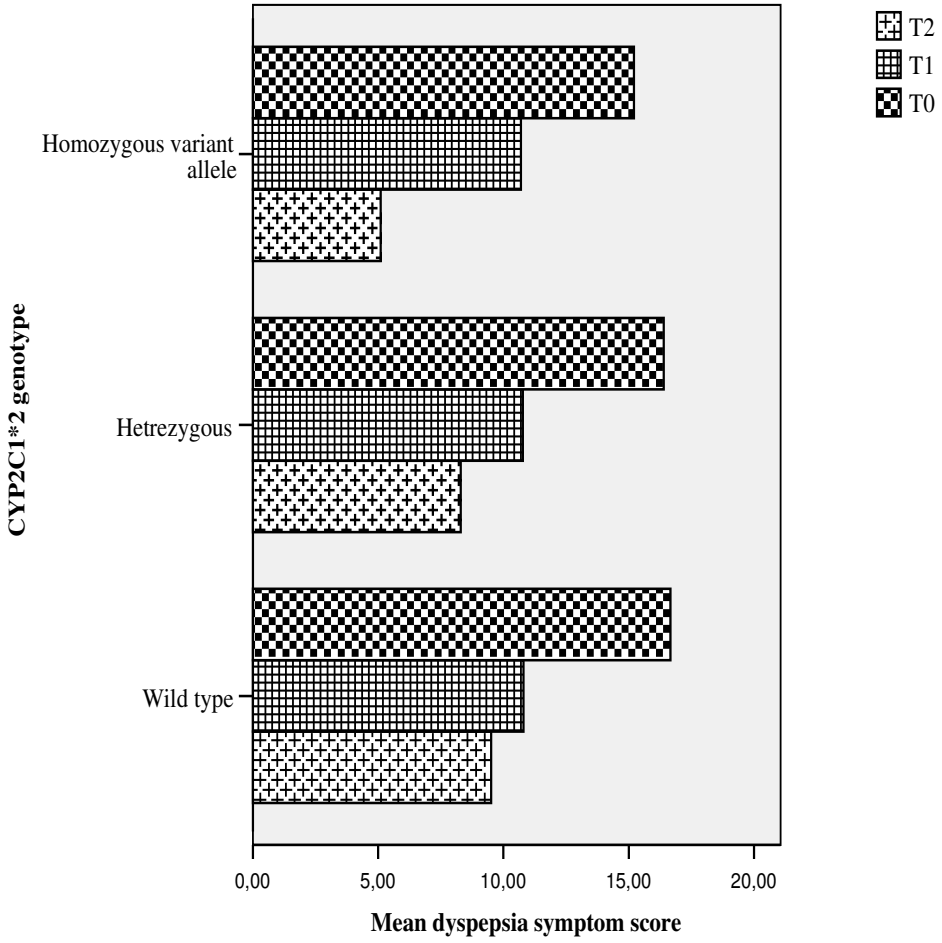
	Success	Failure	Crude OR	95% CI	Adjusted OR	95%CI
N (%)	166 (56.7)	127 (43.3)				
Gender						
Female (%)	54.2	55.1	1			
Male (%)	45.8	44.9	1.04	0.65-1.65	1.01	0.62-1.63
Age in years (mean,sd)	48.4 (15.5)	47.2 (13.4)	1	0.99-1		
<= 45 years (%)	45.2	46.5	1			
> 45 years (%)	54.8	53.5	1.05	0.66-1.67	0.85	0.52-1.38
H. pylori						
Negative (%)	66.9	66.1	1			
Positive (%)	33.1	33.9	0.97	0.59-1.58	0.96	0.57-1.60
Genotype						
RM (%)	55.3	44.7	1			
IM (%)	58.7	41.3	1.15	0.67	1.16	0.67-2.01
PM (%)	70,0	30,0	1.9	0.47	1.63	0.4-6.71
IM+ PM (%)	60,0	40,0	1.2	0.73		
G allele (%)	(81%)	(84%)	1			
A allele (%)	(19%)	(16%)	1.38	0.88-2.17		
GI symp.score (max 48) (mean,sd)	15.4 (6.2)	18.0 (6.7)	0.94	0.9-0.97	0.94	0.90-0.97
0-13 (%)	34.3	28.3	1			
14-19 (%)	39.8	30.7	1.1	0.6-1.9		
20-max (%)	25.9	41,0	0.5	0.3-0.9		
Co-medication				0.6-1.9		
Metabolisation by CYP2C19 (%)	11.4	11	1.04	0.5-2.2		
Metabolisation other pathway (%)	88.6	89	1		1.04	0.49-2.20

Table 3: Mean GI symptom score at baseline, two and four weeks after start treatment in three genotype groups and percentage of decrease in mean GI symptom score in three genotype groups 2 and 4 weeks after start PPI treatment compared to baseline symptom score

	Baseline (T0) **n=293**	**After 2 weeks (T1)** **n=284**	Symptom reduction from baseline (%)	**After 4 weeks (T2)** **n=284**	Symptom reduction from baseline (%)
RM mean (sd)	**16.7 (6.4)**	**10.6 (6.8)**	36.5	**9.3 (6.4)**	44.3
IM mean (sd)	**16.4 (7.0)**	**10.8 (6.5)**	34.1	**8.4 (6.5)**	48.7
PM mean (sd)	**15.2 (7.4)**	**10.4 (5.9)**	31.6	**5.2 (3.8)**	65.8
IM+PM mean (sd)	**16.3 (7.0)**	**10.8 (6.4)**	33.7	**8.0 (6.3)**	50.9

Of those, 70% were treated successfully and symptom reduction was approximately 65% as compared to baseline symptom score. Higher success in this case could be due to genotype related slower metabolism of PPI and as a consequence prolonged acid suppression. Nevertheless, since the frequency of homozygous CYP2C19*2 genotype among Caucasians is very low (on average 3%) this cannot be considered as a relevant factor in the treatment of dyspeptic patients.

Figure 2. Mean GI symptom score at baseline, two and four weeks after start treatment in three genotype groups and percentage of decrease in mean GI symptom score in three genotype groups 2 and 4 weeks after start PPI treatment compared to baseline symptom score. Test for trend in symptom decrease for T1 (p=0.9) and for T2 (p=0.02)



Several studies (38-40) reported significant differences between intragastric pH and plasma drug concentration in GERD patients who have wild type genotype as compared to patients who are homo- and heterozygous for the variant allele. This suggests that patients with IM and PM phenotype might benefit faster and better from PPI treatment. Two studies, however, reported that even though intragastric pH suppression was higher in patients with variant allele, this had no effect on healing

rate of reflux oesophagitis (41), oesophageal acid exposure and reflux symptoms (42).
Indeed, in this study we demonstrated that severity of symptoms, and not CYP2C19*2 genotype predicts treatment outcome. This confirms earlier reports that dyspeptic symptom severity is associated with frequent consultations that are due to inadequate treatment results (43-45).

Our study has certain limitations. First, conclusions regarding the differences between the three genotype groups should be drawn with caution, as the number of patients homozygous for variant allele in our random sample of primary care patients with dyspepsia was small. Altogether the trend of our results should not go unnoticed, and analyses in larger populations might provide more definitive conclusions.
Secondly, although we implicated that wt/wt, wt/*2, and *2/*2 genotypes result in RM, IM and PM phenotype, we did not perform phenotyping by measuring serum half-lives of pantoprazole to confirm this. Therefore, we cannot exclude misclassification of the patients due to possible phenocopies, even though we corrected for use of co-medication that is also metabolised by CYP2C19.
Thirdly, recent investigation by upper gastrointestinal endoscopy was an exclusion criterion and a diagnosis of acid related disorder was based on the symptoms and not on endoscopic diagnosis. Therefore, we cannot distinguish between patients with organic dyspepsia (e.g. GERD) and functional dyspepsia, which might influence treatment outcome.

In conclusion, CYP2C19*2 polymorphism causes slower PPI metabolisation and is related to better treatment efficacy in PPI treatment. Our findings do support the hypothesis that the “Poor Metabolizer” genotype status is associated with increased treatment success. Because of the low prevalence of “Poor Metabolizers” in our dyspeptic patient group, the severity of dyspeptic symptoms appears to have more impact on PPI treatment success in primary care. Therefore, the clinical relevance of our findings for dyspepsia management in daily practice needs to be confirmed.

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Chapter 5

Serotonin receptor 3A polymorphism C178T is associated with severe dyspepsia

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Abstract

Background: Visceral hypersensitivity plays an important role in the aetiology of upper gastrointestinal symptoms. Serotonin (5-HT) modulates visceral sensitivity of the GI tract by its action on 5-HT3 receptors. The action of 5-HT is terminated by 5-HT transporter (SERT) mediated uptake. Genetic polymorphisms influence the function of the 5-HT3 receptor and serotonin availability. Functional polymorphisms have been identified in genes encoding the 5-HT3 receptor A subunit (C178T), and SERT (44 bp insertion/ deletion in promoter region). The influence of genetic variants on 5-HT3 receptor and SERT function may affect upper GI symptomatology.

Aims and Methods: We aim to investigate the association between functional polymorphisms in genes coding for SERT and HTR3 receptor A subunit, and upper GI symptom severity. The data from 592 unrelated, Caucasian, primary care patients with dyspepsia participating in a randomised clinical trial comparing step-up and step-down antacid drug treatment (The DIAMOND trial) were analysed. Patients were genotyped for HTR3A C178T by molecular beacon assay. PCR and subsequent gel electrophoresis was used for genotyping the insertion/deletion polymorphism in the promoter of SERT (SERT-P). The intensity of 8 dyspeptic symptoms at baseline was assessed using a validated questionnaire (0=no; 6= very severe). Patients were considered to have severe symptoms if their sum score was ≥20. Odds ratios were calculated for association between genotype and phenotype.

Results: HTR3A C178T allele carriers were more prevalent in patients with severe dyspepsia (odds ratio (OR) of 1.5; 95% CI 1.05-2.10). This association appeared to be stronger in females (OR 1.9 (1.2-3.1)) than in males (OR 1.04 (0.6-1.8)) and patients homozygous for the insertion/insertion SERT-P genotype (OR 2.05 (1.07-3.92). Females with insertion/insertion SERT-P genotype showed the highest association (OR 3.6 (1.5-8.6)) suggesting an additive effect of these two genes. We did not observe an association between SERT-P genotype considered as a single factor and dyspeptic symptom severity.

Conclusion: The C178T polymorphism in the 5HT3A receptor gene is associated with severe dyspeptic symptoms.

Introduction

Upper gastrointestinal (GI) symptoms are common in the general population, accounting for 3-8 % of the consultations in general practice (1-3). Although it is not a life threatening condition, dyspepsia represents a significant and costly health problem with substantial negative impact on quality of life and health care consumption (4-6).

It is increasingly recognized that visceral hypersensitivity plays an important role in the aetiology of upper gastrointestinal symptoms (7;8). A variety of distinct abnormalities in gastrointestinal motility have been identified in subgroups of patients with upper gastrointestinal symptoms (9-11). Altered processing of afferent information at the peripheral and central level as a consequence of chronic irritation or inflammation may cause visceral hypersensitivity (8;12). There is also evidence for a genetic predisposition. The homozygous C genotype of the C825T polymorphism in the gene encoding the G protein β3 subunit was found to be associated with the presence of unexplained upper abdominal symptoms (13). Taking into account not merely the presence but also the severity of symptoms has revealed the association between pathophysiological mechanisms and the dyspeptic symptom pattern (7;14;15)

The factors that determine upper gastrointestinal symptom intensity are still poorly defined.

Genetic factors may contribute to the risk of having increased visceral sensitivity and consequently affect the intensity of dyspepsia. Since serotonin (5-HT) plays a key role in regulating gastrointestinal sensory function, genes of the serotonergic system are critical candidates in assessing the role of genetic factors in upper GI symptom severity (16-18). The HTR3 receptors play an important role in visceral hypersensitivity (19). They are activated by gastro duodenal distension, after meal or by chemical stimulation. A 5-HT3 antagonist is reported to reduce visceral sensitivity resulting from mechanical or chemical stimulation of visceral afferents in IBS patients (20;21). Serotonin receptors 3 are a legand-gated ion channels. There are five different subunit genes HTR3a-e. The subunit composition influences the biophysical and pharmacological properties of the receptor (22;23). To date, most intensively described are functional channels composed of either homomeric assembly of HTR3A or a heteromeric assembly of HTR3A and HTR3B subunits. The A and the B subunits have different affinity to serotonin (5-HT). Functional polymorphism in the HTR3A gene (C178T) promotes translation of the HTR3A

transcript resulting in enhanced production of the 5-HT3A subunit which have lower affinity for 5-HT and desensitize more rapidly as compared to heteromeric 5-HT3A/3B receptors (23).

Serotonin reuptake is mediated through the serotonin reuptake transporter (SERT) which plays a critical role in the termination of serotonergic neurotransmission. A common polymorphism has been described in this gene (19;24-27). A 44 base pair (bp) insertion or deletion polymorphism in the promoter (transcriptional control region) of the serotonin reuptake transporter (SERT-P), creates a long (l) and a short (s) allele. Homozygousity for the short variant and heterozygousity result in reduced transcription, less protein expression and less reuptake of serotonin (24-27). The short allele of SERT-P polymorphism has been associated with diarrhoea predominant irritable bowel syndrome (D-IBS) and with depression and anxiety related traits (28;29). Based on this information, it can be hypothesised that polymorphisms in HTR3 and SERT gene might influence the motor-sensory processes in the GI tract and influence to upper GI symptom generation.

In the present study we aim to investigate the association between polymorphisms in the genes encoding for the 5-HT3a receptor and 44 bp insertion/deletion polymorphism in SERT and dyspeptic symptom severity in primary care patients with uninvestigated dyspepsia. This association is studied in the knowledge that psychosocial co morbidity and coping styles should be included as potential confounders (30;31).

Methods

Study population

We performed a cross-sectional analysis of patients consulting with dyspepsia who were included in a large multicenter randomised treatment trial in primary care (DIAMOND trial). All patients included were consulting their General Practitioner with a new episode of dyspepsia, without alarm symptoms. They represent patients with dyspepsia managed in primary care. Details of the study design have been described elsewhere (32). The study has been approved by the Medical Ethics Committees of the University Medical Centres Utrecht and Nijmegen.

Data collection

Patients were enrolled after giving written informed consent. All data used for this study were registered at inclusion, before starting dyspepsia treatment. Self-reported questionnaires regarding gastrointestinal symptoms, demographic data (age, gender

and ethnicity) psychopathology, life style factors; current smoker (yes/no) and current alcohol consumption (yes/no), use of co-medications, Irritable bowel syndrome (IBS) status (self reported; yes/no) were obtained at baseline. One blood sample was drawn for DNA extraction and determination of genotypes.

Assessment of dyspeptic symptoms

Dyspeptic symptoms were classified with a dyspepsia symptom questionnaire, validated by Veldhuyzen van Zanten (33). It covers eight essential dyspeptic symptoms: epigastric pain, burping/ belching, heartburn, bloating, flatulence, sour taste, nausea and halitosis. Severity of symptoms was registered on a 7 point Likert scale graded: (0) none, (1) minimal, (2) mild, (3) moderate, (4) moderately severe, (5) severe, (6) very severe. The symptom severity score is calculated by the sum of all items (range 0-48). Patients were classified as having mild, moderate and severe symptoms based on tertiles in the mean symptom score. Severe dyspeptic symptoms were defined as score ≥20.

Assessment of psychological problems

Psychological problems were assessed using a validated Dutch version of SCL-90 questionnaire consisting of 90 questions about 9 dimensions of psychological state. In this analysis we used the SCL-90 dimension "psycho-neuroticism" which summarizes psychic dysfunction (calculated as a sum of all questions divided by the number of dimensions) (34).

Coping style

Coping styles were measured by a short version of the Utrecht Coping Questionnaire consisting of 17 items (35). Six coping styles are distinguished, classified as: active coping, seeking support, avoidance coping, palliative coping, religious coping and passive reaction. Coping styles were rated on a four-point Likert scale ranging from (1) seldom or never, (2) sometimes, (3) often and (4) very often. Scale scores are the sums of the individual items. Higher scores indicate that the specific coping style is more often adopted.

Genotyping

Genomic DNA was extracted from whole blood using the QIAamp DNA blood minikit (Qiagen, Hilden, Germany). Genotyping of the HTR3A C178T polymorphism (rs1062613) was performed by Molecular Beacon assay using the iCycler iQ real-time PCR detection system (BioRad, Hercules, CA, USA). The assay was carried out in a total volume of 25 µl, containing 50 ng of genomic DNA, 12.5 µl 2x iQ Supermix (BioRad, Hercules, CA, USA), 1000 nM of forward primer (5'-GCAGCCTCAGAAGGTGTG-3'), 250 nM of reverse primer

(5'-CAGTTGAAGTCGTCGTAGCC-3') and 400 nM of each molecular beacon. MgCl2 was added to obtain a final concentration of 4 mM. Sequences of the molecular beacons were 5'-FAM-CGGACCAGTGCTCAGGGCGAGGCGGTCCG-DABCYL-3' (C-allele specific) and 5'-TXR-CGCGACCGAGTGCTCAGGACGAGGCTGGTCGCG-DABCYL-3' (T-allele specific).

The PCR thermal cycling protocol applied consisted of an initial denaturation and enzyme activation step of 95°C for 3 min, followed by 40 cycles of 95°C for 30 s, 60°C for 1 min and 72°C for 45 s. In each run several controls were included: a "no template" control to check for contamination of reagents and positive controls for all three genotypes. To validate genotyping of HTR3A C178T by molecular beacon assay, sequencing was performed in a set of randomly chosen patients; concordance was 100%.

Genotyping of SERT-P polymorphism was performed by PCR and subsequent agarose gel electrophoresis. PCR was performed using the primers described by Camilleri et al. (28).

The assay was carried out in a total volume of 25 µl, containing 50 ng of genomic DNA, 12.5 µl GC buffer I, 4.0 µl dNTP mix (2.5 mM each), 200 nM of each primer and 0.25µl TaKaRa LA Taq polymerase (5U/µl). The PCR thermal cycling protocol applied consisted of an initial denaturation step of 94°C for 1 min, followed by 30 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 2 min and a final extension step at 72°C for 5 min. The size of the amplified fragments was determined by electrophoresis on a 2.5% low range ultra agarose gel (Biorad, Hercules, CA, USA) stained with ethidium bromide; 572 bp and 528 bp products were typed as long (L) and short (S) alleles respectively.

Data analysis

All statistical analyses were performed with SPSS for Windows, version 14.0

Severity of dyspeptic symptoms was dichotomised as a sum score of ≥20 yes/no. Patients with 1 or 2 variant alleles (C/T; T/T) were analysed as one group versus patients homozygous for C allele which was most common. In vitro studies have revealed that both the heterozygous (L/S) and homozygous S genotypes of SERT-P result in reduced SERT protein expression and uptake of serotonin (Lesch et al., 1996, Science, 274: 1527-31). The significant difference in amygdaloid activity in subjects with CC and CT genotypes of HTR3A C178T suggests a dominant effect of the T allele (Iidaka et al., 2005, J Neurosci, 25: 6460-6). Therefore, we have

analysed the CC genotype versus the combined homozygous and heterozygous T genotype. Age was categorised as ≤ 45 and > 45 years.

X^2-test was used to test differences in genotype distributions, demographic, lifestyle and biologic factors, between patients with severe dyspepsia and mild and moderate dyspepsia.
To assess association between genotype and phenotype logistic regression model with severe dyspeptic symptoms (yes/no) as dependent variable was used.
For this model adjustments were made for age, IBS status, psycho neuroticism, use of antidepressant medication, use of acid suppressive medication and active coping style. Confounding effect by gender, psycho neuroticism, SERT-P genotype, alcohol use and smoking status was evaluated using stratified analyses.
To avoid bias due to race related differences in genotype distribution we excluded non Caucasian patients from the analysis.
To prevent bias from missing values (4-15%) due to full or partial non response, regression method was used to impute missing values on the items of SCL-90, gastrointestinal symptom questionnaire, and other covariates.
The genotype distributions for the HTR3A C178T and SERT-P polymorphisms were tested for Hardy-Weinberg equilibrium using the Chi square test. P value below 0.05 is considered significant.

Results

From the 664 patients included in the DIAMOND study, 625 (94,1%) were of Caucasian origin. Blood samples for genotyping were obtained from 592 patients (94,7%). No significant difference was observed between genotyped and non genotyped persons with respect to characteristics presented (table 1). Between 20-30% of the patients graded their symptoms as mild to moderate (table 2)
Patients with severe dyspepsia were younger ($p<0.05$) and had higher level of psycho neuroticism ($p<0.05$) than patients with mild and moderate dyspepsia (table 1) No significant difference was observed regarding gender, smoking behaviour and IBS co morbidity, as well as alcohol consumption and co-medication use.
The genotype distributions of HTR3A C178T and SERT-P (table3) were in concordance with Hardy-Weinberg equilibrium. HTR3A 178T allele was more prevalent among patients with severe dyspepsia (45.2 vs. 35.7%), the OR for association was 1,5 (95%CI 1,05-2,1) table 3b). We did not detect association of

Table 1: Patients characteristics according to dyspeptic symptom severity

			Severe dyspeptic symptoms	
		Total	Yes	No
N (%)		592	197 (33.3)	395 (66.7)
Age categories	< 45(%)	259 (43.8)	108 (54.8)	151 (38.2)
	≥ 45(%)	333 (56.2)	89 (45.2)	244 (61.8)
Gender	Male (%)	270 (45.6)	84 (42.6)	186 (47.1)
	Female (%)	322 (54.4)	113 (57.4)	209 (52.9)
Current Alcohol use	Yes (%)	444 (75)	149 (75.6)	295 (74.7)
	No (%)	148 (25	48 (24.4)	100 (25.3)
Current smoking	Yes (%)	160 (27)	59 (29.9)	101 (25.6)
	No	432 (73)	138 (70.1)	294 (74.4)
IBS	Yes	27	10 (5.1)	17 (4.3)
	No	565	187 (95.7)	378 (94.9)
Co-medication	No	388	123	265
	Antacids	115	47	68
	NSAID's	89	24	65
	Antidepresants	36	17	19
Psycho neuroticism	Yes	202 (34.1)	95 (48.2)	107 (27.1)
	No	390 (65.9)	102 (51.8)	288 (72.9)

SERT-P genotype considered as a single factor with dyspeptic symptom severity (table 3b).

To determine whether gender, SERT genotype, smoking and alcohol consumption and psycho neuroticism modify effect of HTR3A C178T genotype on dyspeptic symptoms we stratified for these factors. A significantly increased risk was found in females [(OR 1.9; 95%CI 1.2-3.1) table 4a)] and in patients homozygous for (ins/ins) SERT-P genotype [(OR 2.05 95%CI 1.07-3.92) table 4b)]. The effect of homozygous L SERT-P genotype appeared to be more pronounced in females [(OR 3.6; 95%CI 1.5-8.6) table 5a)]. In males we found risk for ins/ins genotype OR 1.01 (95%CI 0.37-2.75) and for variant allele (ins/del and del/del) OR 1.06 (95%CI 0.56-1.98) table 5b.

Table 2: Overview and grading of dyspeptic symptoms in the study population

Symptom	Absent 0	Min-mal	Mild	Moderate	Moderately severe	Severe	Very severe
Epigatric pain (%)	14.3	11.1	26.5	30.4	13.9	3.2	0.6
Heartburn (%)	16.0	12.3	19.4	22.7	20.1	6.3	3.2
Regurgitation (%)	17.2	14.2	25.3	21.5	15.1	4.7	2.1
Nausea (%)	35.8	22.3	22.1	9.2	6.6	2.9	1.1
Bloating (%)	14.2	13.9	23.2	21.7	19.0	6.2	2.0
Belching (%)	13.0	16.7	25.3	21.4	15.7	5.6	2.4
Flatulence (%)	10.2	17.8	30.7	22.0	13.7	4.5	1.1
Halitosis (%)	42.0	25.6	16.4	8.6	3.6	2.4	1.4

Table 3: (a) SERT and 5HT3a HTR3A C178T and SERT-P genotype distributions. (b) Distribution of genotypes according to the dyspeptic symptom severity. Crude and adjusted OR' for association are presented.

A			N (%)
			592
Genotype			
HTR3A C178T	Wild type (C/C)	n (%)	362 (61.1)
	Heterozygous (C/T)	n (%)	200 (33.8)
	Homozygous (T/T)	n (%)	30 (5.1)
SERT-P	Wild type (ins/ins) n (%)		170 (28.7)
	Heterozygous (ins/del) n (%)		310 (52.4)
	Homozygous (del/del) n (%)		112 (18.9)

B			Severe dyspeptic symptoms	
Symptom	N (%)	592	Yes	No
Genotype			197 (33.3)	395 (66.7)
5HT3a	Wild type n (%)	362 (61.1)	108 (54.8)	254 (64.3)
	T allele carriers n (%)	230 (38.9)	89 (45.2)	141 (35.7)
OR (95% CI)	Crude		1.5 (1.05-2.1)	
OR (95% CI)	Adjusted*		1.5 (1.06-2.2)	
SERT-P	Wild type n (%)	170 (28.7)	59 (29.9)	111 (28.1)
	Variant allele's n (%)	422 (71.2)	138 (70.1)	284 (71.9)
OR (95% CI)	Crude		0.9 (0.6-1.3)	
OR (95% CI)	Adjusted*		0.9 (0.6-1.4)	

•adjusted for age, IBS status, psycho neuroticism, use of anti depressive and use of acid suppressive medication and active coping style

Table 4: Association between severe dyspeptic symptoms and 5HT3a HTR3A C178T genotype stratified by gender (a) and or SERT-P genotype (b)

A	Gender			
	Female		Male	
	Severe dyspeptic symptoms		Severe dyspeptic symptoms	
5HT3a	Yes	No	Yes	No
Wild type (T/T)	56 (49.6)	137 (65.6)	52 (61.9)	117 (62.9)
Variant alleles	57 (50.4)	72 (34.4)	32 (38.1)	69 (37.1)
OR	1.9		1.04	
95% CI	1.2-3.1		0.6-1.8	

B	SERT-P			
	Ins/Ins		Ins/del & del/del	
	Severe dyspeptic symptoms		Severe dyspeptic symptoms	
5HT3a	Yes	No	Yes	No
Wild type (T/T)	31 (52.5)	77 (69.4)	77 (55.8)	177 (62.3)
Variant alleles	28 (47.5)	34 (30.6)	61 (44.2)	107 (37.7)
OR	2.05		1.31	
95% CI	1.07-3.92		0.87-1.98	

Discussion

The results of this study suggest that patients who have HTR3A 178T polymorphism are at increased risk of having severe dyspeptic symptoms. This risk seems to be even higher for women and patients homozygous for long allele of SERT 44 bp ins/del polymorphism.

The association could be explained as follows;

Noxious and non-noxious visceral sensations are carried by extrinsic primary afferents to the dorsal horn of the spinal cord. Sensory transmission in the spinal dorsal horn is attenuated by endogenous inhibitory systems that originate at the brain stem. One of the main descending systems to the spinal dorsal horn is serotonergic (36). 5-HT3 receptors present on spinal inhibitory interneurons receive input from the descending serotonergic fibers. Activation of these 5-HT3 receptors evokes release of GABA, which in turn reduces the excitability of dorsal horn neurons (37). Consequently, the output of visceral sensory information to the brain stem and

thereby symptom perception is reduced. It has been demonstrated in a model of visceral pain that 5-HT3 receptors in the spinal cord mediate antinociception (38).

Table 5: OR's for association between severe dyspeptic symptoms and 5HT3a HTR3A C178T genotype stratified by SERT genotype in females (a) and males (b)

A	SERT-P			
	Wt/Wt		Variant allele	
	Severe dyspeptic symptoms		Severe dyspeptic symptoms	
5HT3a	Yes	No	Yes	No
Wild type (T/T)	16 (45.7)	45 (75.0)	40 (51.3)	92 (61.7)
Variant alleles	19 (54.3)	15 (25.0)	38 (48.7)	57 (38.3)
OR	3.6		1.5	
95% CI	1.5-8.6		0.9-2.7	

B	SERT-P			
	Wt/Wt		Variant alleles	
	Severe dyspeptic symptoms		Severe dyspeptic symptoms	
5HT3a	Yes	No	Yes	No
Wild type (T/T)	15 (62.5)	32 (63.0)	37 (62.0)	85 (63)
Variant alleles	9 (37.5)	19 (37.0)	23 (38.0)	50 (37.0)
OR	1.01		1.06	
95% CI	0.37-2.75		0.56-1.98	

Thus, the increased expression of 5-HT3A subunits in HTR3A 178T allele carriers may result in a higher proportion of homomeric 5-HT3A receptors and as a consequence decreased response to 5-HT of the 5-HT3 receptor involved in the descending antinociceptive pathway reflected in higher symptom severity. The additive effect of the LL genotype of the SERT-P polymorphism is conceivable as homozygosity for the long allele results in more rapid re-uptake of 5-HT and earlier termination of 5-HT induced signalling. As a consequence activation of the 5-HT3 receptor on inhibitory interneurons in the spinal cord is even more diminished; this reduces antinociception.

The association between severe dyspeptic symptoms and the HTR3A C178T and SERT-P genotypes appears to be stronger in females than in males. A possible explanation for this finding would be different availability of serotonin in males and females. Indeed, it has been reported that rate of 5-HT synthesis in central nervous system (CNS) is more than 50% higher in males than in females (39) The lower

level of 5-HT available for receptor activation in females is consistent with reduced 5-HT3 receptor mediated antinociceptive effects.
In short, the presence of a 5-HT3 receptor with lower response to 5-HT due to polymorphism, rapid 5-HT re-uptake by SERT and less serotonin available for receptor activation due to gender differences in 5-HT synthesis predisposes to increased perception of visceral stimuli.
Other factors associated with symptom severity were age (< 45 years) and increased level of psycho neuroticism. Dyspeptic symptoms, in particularly epigastric pain (40) and visceral pain perception (41) decrease with age. To date, there is a little evidence about underlying mechanism which can explain this finding, Aging process and age-associated changes (e.g., co morbid diseases) are thought to play role.
Psychological problems are often reported to coincide with (severe) gastrointestinal symptoms (42-44). In this study we confirm this association.

To appreciate results of this study several limitations should be high lightened:
There is a possibility that association between HTR3A 178T allele and severe dyspeptic symptoms is due to the effect of some other gene which is in linkage disequilibrium with HTR3A C178T.
We could not discriminate between patients with organic and functional dyspepsia. This could influence the results if the association would be specific only for one of them.

In conclusion, the results of this study suggest that there is an association between HTR3a 178T allele and severe dyspeptic symptoms. Altered receptor function alone or in combination with SERT-P genotype could explain symptoms severity in a subgroup of patients. Further research will have to replicate this result and clarify the clinical consequences of it.

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Chapter 6

Effectiveness and costs of step-up versus step-down treatment using antacids, H2-receptor antagonists and proton pump inhibitors in patients with new onset dyspepsia - a primary care based randomised trial

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Abstract

Background: Considerable workload and high costs are involved in the management of dyspepsia in primary health care. In spite of consensus statements and guidelines, the most effective and efficient empirical strategy for initial management of dyspepsia remains to be determined.

Methods: We conducted a double-blind randomised trial comparing step-up and step-down treatment strategies for initial management of patients with new onset dyspepsia in primary care. Patients were treated stepwise with antacid, H2-receptor antagonist, and proton pump inhibitor, or the other way around. Each step lasted 4 weeks and treatment only continued with the next step if symptoms persisted or relapsed within 4 weeks. Patients were followed for 6 months.

Results: Between October 2003 and January 2006 a total of 664 patients were randomly assigned to step-up (n=341) or step-down (n=323) treatment. Although the step-down treatment was more effective in the first month, both strategies were equally effective at 6 months (step-up 72%; step-down 70%). However, costs differed between the treatment strategies in favour of the step-up strategy (p=0.02) which was primarily due to costs of medication.

Conclusions: Although step-down results in earlier symptom reduction, step-up is superior in cost-effectiveness for initial treatment of patients with dyspeptic symptoms in primary care.

Introduction

Initial management of dyspepsia remains a challenge to physicians, due to the high prevalence of dyspepsia resulting in high medical workload, considerable impact on quality of life, and important socio-economic consequences.(1-4) Unfortunately, solid evidence to decide on the best initial management strategy still is lacking.(5-8) Most studies reported on single drug comparisons and have primarily been conducted in patients with persisting dyspeptic symptoms referred to secondary care. Up till now, several meta-analyses and reviews have been conducted to address important questions concerning treatment strategies for patients with dyspeptic symptoms.(9-18) The Cochrane review on 'initial management of dyspepsia' demonstrated that only few studies - mostly of inadequate methodology - dealt with initial management of dyspepsia. Authors concluded that considerable gaps in knowledge on the most cost-effective management strategy for uninvestigated dyspepsia exist.(9) Consequently, guidelines for management of dyspepsia are inconsistent.

The AGA and Canadian guidelines recommend empirical proton pump inhibitor for patients with predominant GERD, and test-and-treat followed by empirical proton pump inhibitor for all others.(19;20) According to the AGA, in a population with low H. pylori prevalence empirical proton pump inhibitor is also an initial option. British guidelines state there is currently insufficient evidence to guide which of these two options should be offered first.(21) Scottish guidelines adopt the ROME II definition for dyspepsia, necessitating initial endoscopy for diagnosis. They advise to treat functional dyspepsia functional dyspepsia with antacids or H2-receptor antagonists, followed by test-and-treat when symptoms persist.(22) In contrast, Dutch guidelines recommend empirical treatment with antacids or H2-receptor antagonists for all patients with new onset dyspepsia, and reserve proton pump inhibitor treatment for patients with persisting predominantly GERD symptoms, and test-and-treat for all other patients with persisting symptoms (step-up strategy).(23) The step-down strategy on the other hand, based on initial treatment with proton pump inhibitors, is propagated widely because of its presumed superior cost-effectiveness.(9) In order to improve our insight into this problem we conducted a double-blind randomized trial comparing step-up versus step-down therapy for the initial management of dyspepsia in primary care.

Methods

From October 2003 to January 2006 312 general practitioners agreed to include patients in the DIAMOND study (Dutch study on Initial Management Of Newly diagnosed Dyspepsia). The methodological aspects of the trial are outlined below, and details have been described elsewhere.(24) The protocol of this randomised double-blinded trial was approved by the ethics committees of the University Hospitals of Nijmegen, Utrecht and Maastricht. The trial is registered by ClinicalTrials.gov as NCT00247715. All participants gave written informed consent.

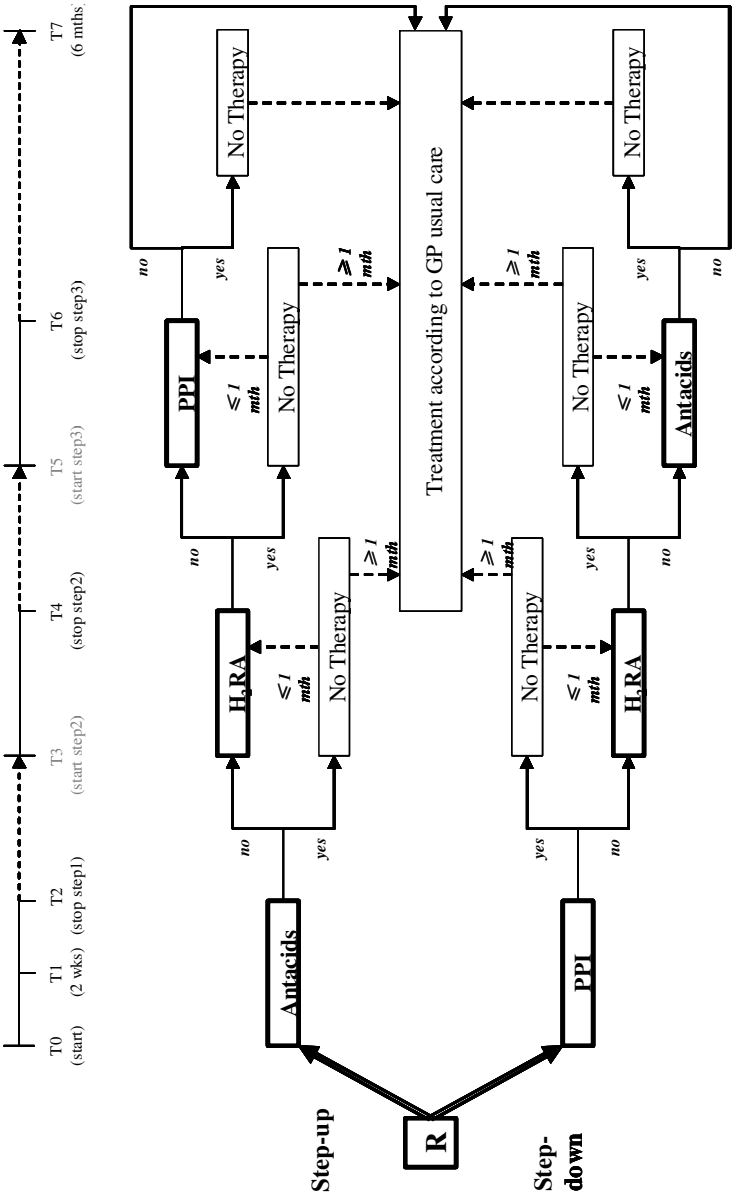
Patients / Entry Criteria

Patients, aged 18 years and older, consulting their general practitioner for new onset dyspepsia were eligible. Dyspepsia was defined as: episodic or persisting pain or discomfort centred in the upper abdomen (epigastria), judged by the physician to originate in the upper gastrointestinal tract, which might be accompanied with symptoms as regurgitation, heartburn, nausea, or bloating.(25;26) New onset dyspepsia was defined as no use of prescribed acid suppressive medication for three months, and no gastroscopy one year prior to randomisation. Exclusion criteria were alarming symptoms (passage problems for food, unintended weight loss, anaemia, vomiting of blood), pregnancy, or insufficient knowledge of the Dutch language.

Study design

Consultations were carried out according to the physician's standard practice. Additionally, patients received information on the trial. Eligible patients were randomly assigned to step-up or step-down treatment (Figure 1), by means of opening one of identically wrapped randomised medication boxes present at the general practice, containing separately wrapped medication packages for each medication step. The randomisation sequence was computer generated with blocks of 6 on a 50/50 basis, and concealed for patients, investigators and study personnel. At the inclusion visit, a blood sample was taken, a 4-weeks follow-up visit was scheduled, the step 1 medication as well as a self-report questionnaire on symptoms and quality of life was handed out. Patients were instructed to fill out this questionnaire before starting the treatment. For the other baseline assessments a questionnaire was send by mail directly after inclusion was reported. If follow-up visits were not usual practice for the general practitioner, patients were instructed to cancel the appointment when they were free of symptoms in order to minimize protocol generated extra consultations. Treatment was only continued with the next step if symptoms were not adequately relieved or relapsed within the next four

Figure 1. Overview of study design



weeks. If symptoms relapsed at a later time, the general practitioner treated according to standard practice. Patients were allowed to proceed to the next treatment step earlier if symptoms worsened or unpleasant side effects occurred. During the follow-up period of six months, questionnaires were sent at 2 weeks (T1), at the end of each treatment step or - in case treatment was no longer required - at intervals of 4 weeks (T2, T4, T6), and at six months (T7). In case of relapse within the next 4 weeks an additional questionnaire was sent to assess the symptom status at the beginning of that treatment step (T3, T5). The double blinding of the treatment was maintained up to 6 months after randomisation.

Pharmacotherapy

Each treatment step provided medication for 4 weeks and consisted of 1] antacids 4 times daily (aluminiumoxide/magnesiumhydroxide 200/400mg); 2] H2-receptor antagonist twice daily (ranitidine 150mg); and 3] proton pump inhibitor once daily (pantoprazole 40mg) for step-up and the other way around for step-down. To maintain blinding antacids were accompanied by a 'proton pump inhibitor-placebo' once daily and proton pump inhibitor by 'antacid-placebo' 4 times daily.

Assessments

Before initiating treatment, type and severity of gastrointestinal symptoms, i.e. regurgitation, heartburn, epigastric pain, nausea, bloating, were assessed on a 7-point adjectival scale(27), and quality of life using the EuroQol-5D.(28;29) Furthermore, demographics, lifestyle habits, work and income, medical history, and medication use at baseline were assessed with the additional self-report postal questionnaire at inclusion. Helicobacter Pylori status (Pyloriset® EIA-GIII, Orion Cooperation Orion Diagnostica, Espoo, Finland) was assessed by IgG antibody-titer assessment in a venous blood sample. Both patient and investigator were blinded to the results of the Helicobacter Pylori test until 6 months after inclusion.

During the follow-up measurements, patients were asked to report adequacy of symptom relief, type and severity of gastrointestinal symptoms (27), quality of life (28;29), lifestyle habits, work absenteeism, out-of-pocket costs, and medication use. A case record form was used to assess general practitioner consultations, adverse events, diagnostics, and referrals. Completeness and correctness of these forms were verified retrospectively for all patients using the general practitioners information system at the end of follow-up.

Costs

The financial estimates used in our study were based on the cost to society according to 2006 prices. The societal viewpoint was considered relevant, because health care

interventions are not confined to the health care system itself, but also influence societal factors. We used a quantity-and-price approach to estimate total costs in Euros, based on primary data from this randomised trial.

Direct medical quantities assumed relevant include acid related medication, consultations, diagnostic tests, and referrals. Non-medical quantities include productivity loss of paid and unpaid work, and out-of-pocket expenses. Valuation of costs was performed according to Dutch guidelines for (farmaco-) economic evaluations in health care.(30) Costs of medication were based on average retail prices for antacids, and standard cost prices for H2-receptor antagonist and proton pump inhibitors.(31;32) General practitioner consultation costs were based on a single consultation of 10 minutes. For diagnostic tests a weighted mean tariff of all tests was calculated based on costs derived from a database on tariffs for medical interventions 2003.(30) Standard cost prices were used for referrals and hospitalisation assuming equal distribution over general and university hospitals. Productivity losses were calculated according to the friction cost-method.(30) Out-of-pocket expenses, including transportation, and dietary changes were reported on the questionnaire. All prices were indexed to 2006 where necessary.

Data analyses

Data were analysed on intention-to-treat principles, including all patients' randomised independent of medication used. Treatment success was defined as adequate symptom relief at six months, indicated with a dichotomous question (yes or no). This subjective judgement of the patients is intentionally chosen, since the decision to continue treatment is generally based on this same judgment. Baseline characteristics and outcomes were compared between the groups using □2-tests and Student's t-test or non-parametrical tests where appropriate. Mann-Whitney-U test were used to compare costs between the treatment strategies. In order to describe the relationship between costs and treatment success, an incremental analysis was performed on the two strategies, using step-up as reference. Sensitivity analyses were performed to study the impact of varying costs on the average costs of the two strategies. All calculations were performed using SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA). All p-values calculated were two-tailed and the alpha level of significance was set at 0.05.

The calculated sample size was based on the assumption of 40% treatment effectiveness (adequate symptom relief) at 6 months in both groups.(33;34) To be able to demonstrate equivalence with a reliability α=0.05, 80% power (β=0.20), and a maximal difference in effectiveness (Δstep-up vs. step-down) of 10% between the

treatment strategies, a total of at least 297 patients needed to be randomised to each treatment group.

Results

One hundred fifty (48%) of the participating general practitioners recruited a total of 664 patients. Three hundred forty-one of these patients were randomly assigned to the step-up and 323 patients to the step-down treatment strategy. A total of 332 (97%) patients in the step-up, and 313 (97%) in the step-down group completed the trial with sufficient data for evaluation. Nineteen patients (step-up n=9; step-down n=10) did not complete the trial (Figure 2). The treatment groups were well comparable at baseline (Table 1). During the study period, respectively 139 (41%), 84 (25%), and 118 (35%) patients assigned to step-up treatment received just one, two, or all three treatment steps. In the step-down group this was 153 (47%), 57 (18%), and 113 (35%) patients respectively. Of these, 11 patients (7 in step-up; 4 in step-down) did not use any medication.

Treatment success after 6 months was similar for the two strategies (step-up: 72%; step-down: 70%; OR: 0.92, 95%-CI:0.7-1.3). Adequate symptom relief up to six months was achieved for step-up in 80 (24%) and step-down in 78 (25%) of the patients after treatment with only one treatment step; in respectively 44 (13%) and 26 (8%) of the patients after two steps; and in 24 (7%) and 20 (6%) of the patients after completing all three steps. The other 90 (27%) patients of the step-up, and 95 (30%) of the step-down with adequate symptom relief at six months received additional treatment during the study period or were still using acid suppressing drug at six months. During the study period, treatment effect was reported earlier (statistically significant at two weeks and one month) in patients receiving step-down compared to step-up approach (Figure 3a).

Figure 3a. Time to sufficient symptom relief

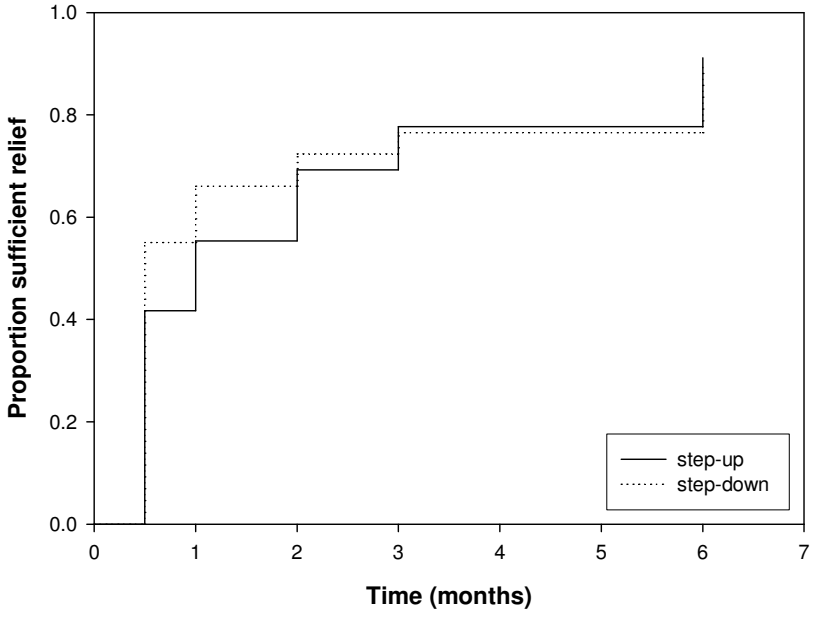
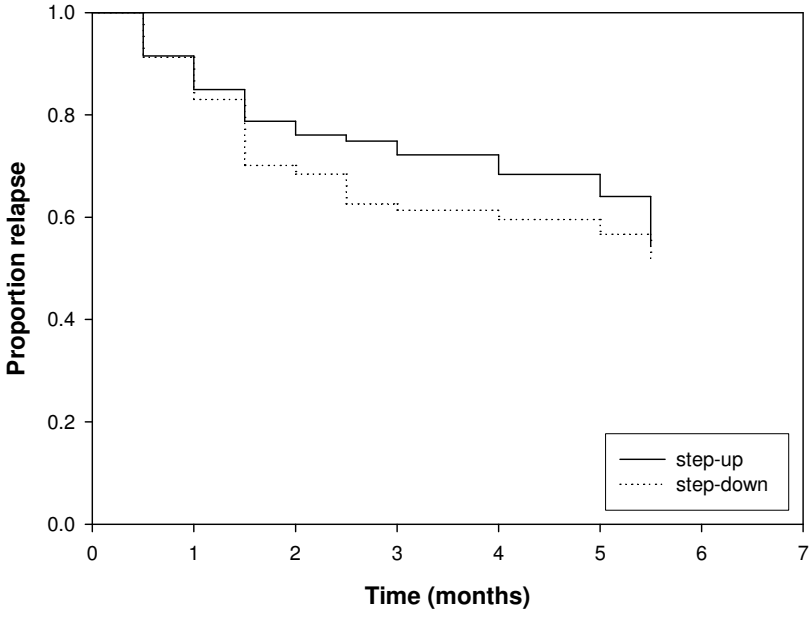


Figure 3b. Time to symptom relapse after initial success



The number of patients with symptom relapse did not differ (p=0.15) between step-up (34% of 306 patients) and step-down (40% of 285 patients). Neither did the relapse period (p=0.16, Figure 3b)

Symptom patterns at entry were similar. Discriminating gastro-oesophageal reflux symptoms from dyspeptic symptoms, 470 (77%) patients reported reflux as well as dyspeptic symptoms, 8 (1%) solely reported reflux symptoms, and 130 (21%) solely dyspeptic symptoms. Reflux symptoms were predominant in 54 (17%) of the step-up and 51 (17%) of the step-down patients. Although treatment success after 6 months was equal for the predominant symptom categories (overall p=0.28), patients

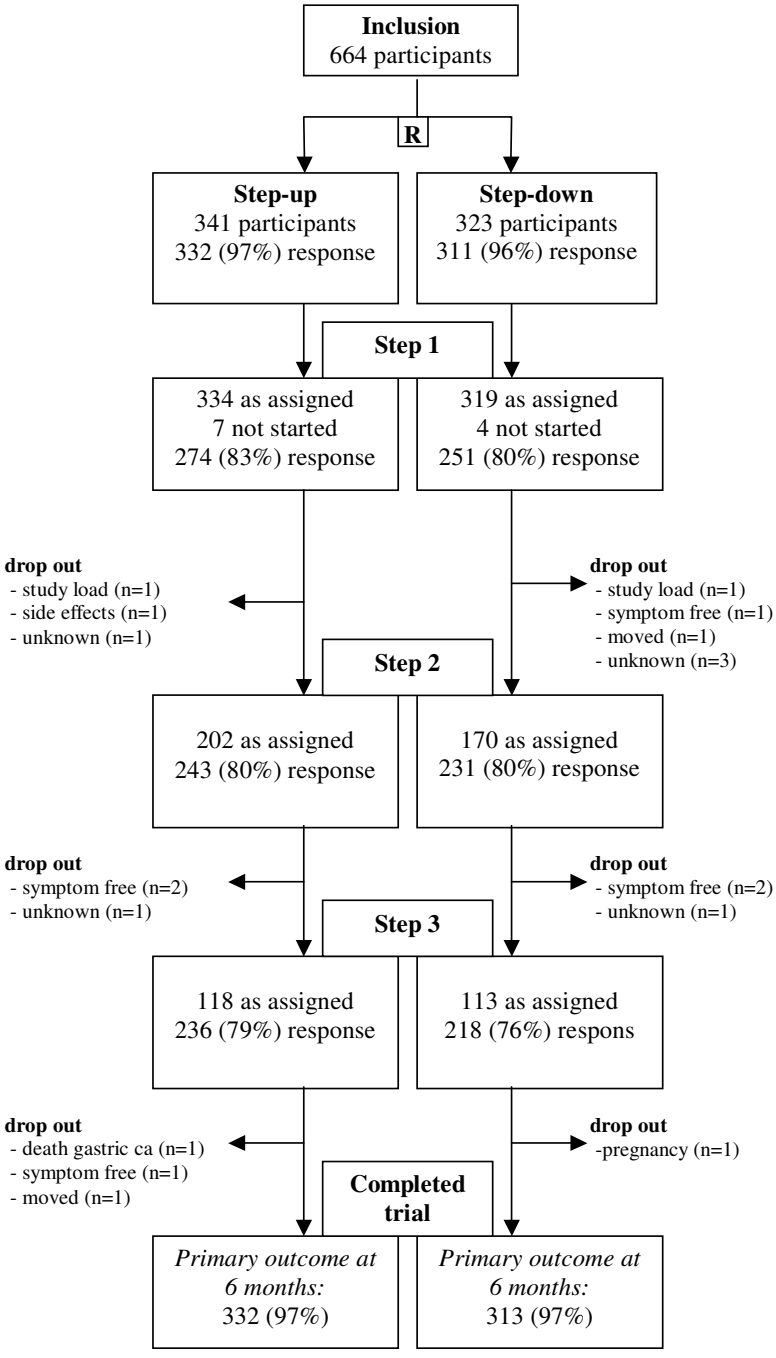


Figure 2. Trial profile

with predominant reflux symptoms tended to respond less effectively to treatment in the step-up (62.3%) as well as the step-down (68.6%) approach (Figure 4b).
Medical consumption differed between the strategies only with regard to prescribed medication (Table 2).

Table 1: Baseline characteristics according to treatment assignment

		Step-up (n=341)	Step-down (n=323)
Gender	Male	157 (46%)	147 (46%)
	Female	184 (54%)	176 (54%)
Age (years)	< 40 years	120 (35%)	108 (33%)
	40 - 55 years	118 (35%)	108 (33%)
	≥ 55 years	103 (30%)	107 (33%)
Ethnicity	Caucasian	317 (93%)	306 (95%)
Work		Paid job	196 (63%)	196 (63%)
Smoking	Current smokers	96 (30%)	79 (26%)
Number of smokes/day	0 - 9	22 (25%)	20 (26%)
	10 - 19	38 (43%)	30 (39%)
	>= 20	28 (32%)	27 (35%)
Alcohol intake	Current drinkers	226 (70%)	234 (77%)
Number of glasses/week	0 - 7	152 (70%)	153 (67%)
	8 - 14	43 (20%)	56 (24%)
	>= 15	22 (10%)	20 (9%)
H. pylori status	Positive	124 (38%)	107 (34%)
Symptoms	Regurgitation	201 (66%)	212 (72%)
	Heartburn	216 (70%)	207 (70%)
	Epigastric pain	215 (74%)	204 (75%)
	Nausea	118 (38%)	134 (46%)
	Bloating	215 (70%)	208 (71%)
Quality of life	EQ-5Dscore (SD)	0.76 (0.19)	0.79 (0.17)
	EQ-5DVAS (SD)	54 (25)	54 (25)

The average calculated medical costs were lower for patients in the step-up compared to the step-down (€228 versus €245; p<0.001), which was solely due to the difference in use of acid suppressing medication (€81 versus €97; p<0.001, Table 3). The costs associated with productivity loss and out-of pocket expenses did not differ between the strategies (p=0.56, Table 3). Combined (direct medical and indirect costs), average costs were 8% higher (€34.50) in patients in the step-down strategy (p=0.02) compared to the step-up strategy. Medical costs accounted for

53% of total expenses in the step-up (€145,184 for treatment of 341 patients) as

Table 2: Six months follow-up data participants according to treatment assignment

		Step-up (n=341)	Step-down (n=323)
Medical outcomes			
Treatment success	Yes	238 (72%)	219 (70%)
	No	94 (28%)	94 (30%)
Symptoms	Regurgitation	70 (27%)	77 (32%)
	Heartburn	90 (36%)	86 (36%)
	Epigastric pain	54 (22%)	60 (25%)
	Nausea	39 (15%)	40 (16%)
	Bloating	93 (36%)	92 (38%)
Quality of life	Worsened (VAS)	36 (15%)	41 (19%)
	Unchanged (VAS)	44 (19%)	35 (16%)
	Improved (VAS)	155 (66%)	144 (65%)
Adverse events	step 1 (n=653)	70 (21%)	65 (20%)
	step 2 (n=372)	18 (9%)	30 (18%)
	step 3 (n=231)	21 (18%)	20 (18%)
Direct medical quantities			
Prescribed trial medication	Antacid	341 (100%)	113 (35%)
	H2-receptor antagonist	202 (59%)	170 (53%)
	Proton pump inhibitor	118 (35%)	323 (100%)
Number of patients using additional treatments	Antacid	54 (16%)	59 (18%)
	H2-receptor antagonist	22 (6%)	30 (9%)
	Proton pump inhibitor	98 (29%)	93 (29%)
	H. pylori eradication	6 (2%)	6 (2%)
	Prokinetics	10 (3%)	6 (2%)
	Other gastrointestinal	25 (7%)	26 (8%)
Number of Consultations	General practitioner #	752	719
	Gastroenterologist	15	16
	Other	4	2
Number of diagnostics tests	H. pylori - test	37	31
	Endoscopy	35	35
	Upper abdominal ultrasound	19	13
	X-oesophagus/stomach	2	4
	Other	17	13
Number of Hospitalisations		8	2
Indirect quantities			
Absenteeism	Number of patients	30 (10%)	30 (10%)
	Number of days	205	200
Productivity loss unpaid work	Number of patients	147(47%)	142 (48%)
	Number of days	1889	2135
Out of pocket expenses*	Number of times reported	39	52

*Out of pocket expenses include transportation, and costs for changed diet. #Excluding first consult

well as step-down (€148,664 for treatment of 323 patients) strategy. The 8% higher total costs (€426 versus €460) and non-significant lower success rate (2%) for step-down resulted in a dominant incremental cost-effectiveness ratio for step-up.

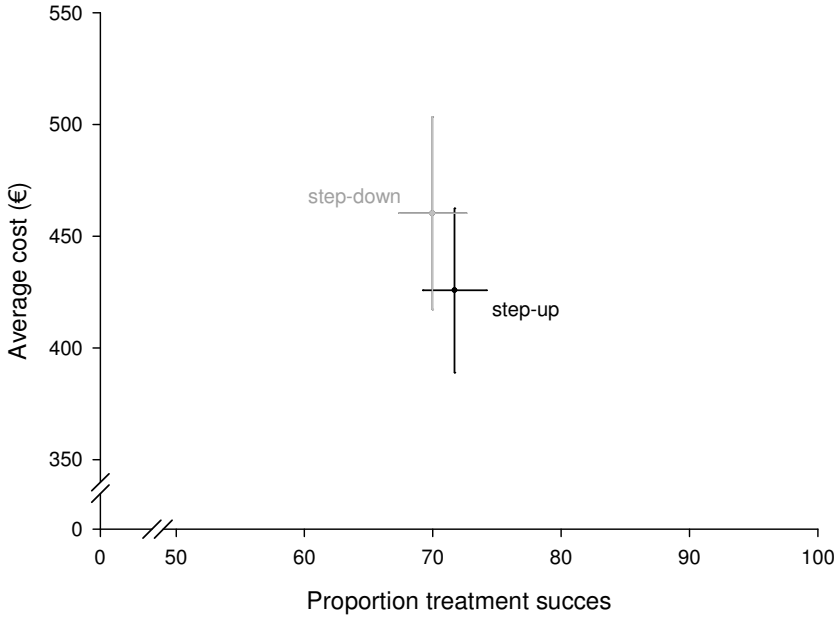
The cost-effectiveness of the dyspepsia treatment strategies was sensitive to the price of medication. When cost calculations were performed using cost prices of generic drugs instead of specialities, the difference in medication costs remained ($p<0.001$), but average medical costs ($p=0.06$) and overall average costs ($p=0.78$) were no longer significantly different between the strategies.

Table 3: Average costs according to treatment assignment

		Step-up (n=341) Mean	Step-down (n=323) Mean	p-value
Direct Medical Costs (n=664)				
Prescribed trial medication	Antacid	23.51	8.22	<0.001
	H2-receptor antagonist	13.02	11.57	0.09
	Proton pump inhibitor	15.68	45.30	<0.001
Additional medication	Antacid	1.74	1.76	0.46
	H2-receptor antagonist	1.13	1.88	0.15
	Proton pump inhibitor	22.05	25.74	0.82
	H. pylori eradication	3.59	2.84	0.93
Total medication (average)		80.71	97.31	<0.001
Consultations	General practitioner	67.41	67.84	0.97
	Gastroenterologist	2.77	3.12	0.73
	Other	0.74	0.39	0.45
Total consultations (average)		70.92	71.36	0.95
Diagnostics tests	H. pylori - test	3.24	2.87	0.97
	Endoscopy	55.09	58.16	0.64
	Ultrasound	7.63	5.51	0.44
	X-oesoph./stomach	1.22	2.57	0.38
	Other	8.97	7.24	0.90
Total diagnostic tests (average)		76.14	76.35	0.83
Total medical costs (average)		227.77	245.01	<0.001
Indirect Costs (n=606)				
Productivity loss	Paid work	146.71	161.69	0.92
	Unpaid work	64.70	72.19	0.57
Out-of pocket expenses*		4.28	3.41	0.57
Total indirect costs (average)		215.70	237.29	0.56
Average total costs (n=664)		425.76	460.26	0.02

*Out of pocket expenses include transportation, and costs for changed diet.

Figure 4a. Average costs and effectiveness (95%CI) according to treatment assignment

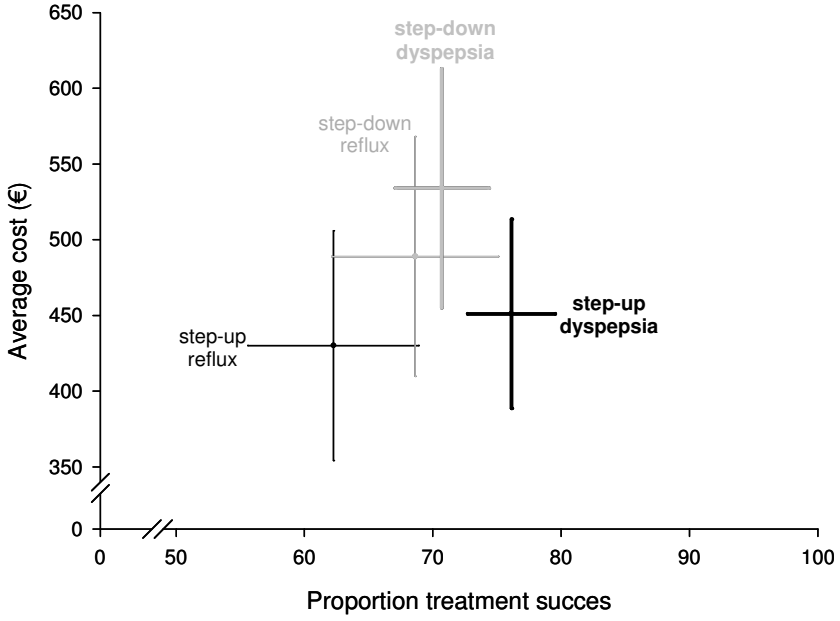


Discussion

Ideal, dyspepsia treatment should quickly and conveniently alleviate patients' symptoms whilst also minimizing the use of healthcare recourses. We have demonstrated that a step-up strategy starting with antacids is more cost-effective than a step-down strategy starting with proton pump inhibitors in the initial management of dyspepsia in primary care. The step-up regimen resulted in slightly lower medical as well as overall costs with equal clinical effectiveness as compared to the step-down approach. Costs were primarily sensitive to prices of medication, minimizing the difference in costs between the strategies when prices of generic medication instead of specialities were regarded.

Although some comparisons of stepwise management strategies have been published before, to our knowledge this is the first primary care based randomised

Figure 4b. Average costs and effectiveness (95%CI) according to treatment assignment and predominance of dyspepsia or reflux



trial directly comparing step-up and step-down treatment strategies as initial management of new onset dyspepsia including dyspeptic symptoms as well as heartburn.(35-39) In prior studies on stepwise management, initial proton pump inhibitor treatment strategies seem to be superior for patients with persistent dyspeptic symptoms.(35-37;39-41) However, these results cannot automatically be extrapolated to other populations, because strategies vary substantially and all but one (36) of the studies were performed in selected groups of patients with GERD or predominant heartburn. Dyspeptic patients generally profit less form proton pump inhibitors as compared to GERD patients. Overall, there is dissimilarity regarding inclusion (20;21;23) or exclusion (19;22) of predominant GERD. Although the AGA and Scottish guidelines recognizes the difficulty for patients to describe their predominant symptom, which may change over time, and the considerable overlap of predominant GERD and epigastric pain in uninvestigated patients, they adopted

the widely accepted ROME II definition to exclude these patients.(14;19;22) The British NICE guideline does not discriminate GERD from dyspepsia, while the Dutch CBO guideline only makes this distinction for patients with symptoms persisting longer than 2-3 months.(21;23) We included a patient population with both dyspeptic and gastro-oesophageal reflux symptoms, which in our view is a more realistic representation of the patient population with upper abdominal complaints encountered in daily clinical practice. Defining the optimal strategy for management of dyspepsia, provided there is one for all patients, is complicated by the lack of an unequivocal definition the heterogeneity of symptoms and numerous underlying causes in dyspeptic patients.(14;42;43)

The strengths of this trial is the large sample size of 664 patients, the randomised, double-blinded design, the direct comparison of step-up and step-down acid suppressive therapy, and the extensive outcome assessment including costs. Nonetheless, this study also has its limitations. Although efforts have been made to design the study as pragmatic as the clinical trial would allow, differences between the study protocol and actual clinical practice were inevitable.(24) Furthermore, we are unable to assess whether there has been relevant selection of patients. We did not record the characteristics of patients not included in the trial. Finally, it remains unclear if evaluation of cost-effectiveness over a period of 6 months, although longer than in most studies, is adequate for a chronic relapsing condition as dyspepsia.

In conclusion, the step-up approach is more cost-effective at 6 months in patients with new onset dyspepsia than a step-down approach. Nonetheless, patients on initial empirical treatment with proton pump inhibitor (step-down) show an earlier response, especially in the subgroup with predominant reflux symptoms. Based on the perspective of cost-effectiveness, our results provide reasons to reconsider present guidelines for dyspepsia.

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Chapter 7

Determinants of successful acid inhibiting treatment in primary care patients with uninvestigated dyspepsia

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Abstract

Background: Evidence on the most adequate treatment of dyspepsia in general practice still is incomplete. On average only half of the dyspepsia patients in primary care experience symptom relief after treatment with acid inhibitors. Knowledge of determinants of success and optimal duration of treatment could play an important role in properly deciding on the first step of treatment.

Aim: To investigate which demographic, psychosocial, genetic, biological or lifestyle factors are associated with short term success and with (relatively) long term failure of acid inhibitor treatment strategies for uninvestigated dyspepsia..

Methods: We analyzed data of the DIAMOND trial, a randomized clinical trial comparing step-up and step-down antacid drug treatment for patients with new onset dyspepsia. Patients were treated stepwise with antacids; H2RA and proton pump inhibitor (PPI) whereby step-up treatment arm started with antacids and step-down arm with PPI. Treatment success, defined as adequate symptom relief, was evaluated after one and after three months. Dyspeptic symptom severity, psychopathology, major life and coping styles were measured with validated questionnaires. H. pylori status was determined by measuring IgG antibodies in serum. Differences between success and failure groups were evaluated using the chi-square test and Student's t-test. After univariate, multivariate logistic regression analysis was used to assess determinants of treatment success and models were evaluated with ROC-curve analysis.

Results: Between October 2003 and January 2006 a total of 664 patients were randomly assigned to the step-up or step-down treatment arm. Treatment success after one month was achieved in 39,5 % patients with step-up treatment arm and 46,7 % in the step-down arm. After three months success was observed in 80% of all patients. In multivariate analysis we found increased epigastric pain (OR 0.67 (0.67-0.94)), presence of heartburn (OR 0.88 (0.76-1), halitosis (OR 0.79 (0.66-0.94)) and passive coping style (OR 0.45 (0.45-0.88)) to reduce the chances of successful one month treatment with antacids, while a history of psychological problems (OR 2.3 (1.25-4.2)) was associated with a higher treatment success. Treatment success was predicted with this model with an AUC of 0.67 (0.61-0.73). Epigastric pain (OR 0.77 (0.64-0.92)) and flatulence (OR 0.82 (0.68-0.98) were found to reduce the probability of PPI treatment success, while presence of the HTR3A 178T polymorphism (OR 1.7 (1.1-2.8)) and the use of a palliative coping style (OR 1.24 (1.02-1.5)) were positively associated with PPI treatment success. This model predicted treatment success showing an AUC of 0.66 (0,59-0.72). Presence of nausea (OR 1.24 (1.1-.4) was associated with treatment failure of any antacid treatment after 3 months. However, the AUC of the model on failure with any treatment was lower (0.59 (0.53-0.64)).

Conclusion: The type of dyspeptic symptoms does influence antacid treatment response. Patients with epigastric pain do need more than 4 weeks of antacid treatment, while those with nausea are less likely to respond to any antacid treatment.

Introduction

Dyspepsia is one of the most common functional gastrointestinal disorders (FGID). (1;2) It refers to a symptom complex thought to arise in the upper gastrointestinal tract and includes symptoms such as heartburn, acid regurgitation, excessive burping or belching, a feeling of slow digestion, early satiety, nausea and bloating.(3) The population prevalence ranges from 25-40% worldwide.(4) Dyspepsia is a significant health problem with substantial impact on quality of life and health care costs.(5-7)
The aetiology of the syndrome is complex; hyperacidity, delayed gastric emptying, duodenal reflux and psychological factors are suggested to be involved in symptom development ((8-11). Up to 25% of the dyspeptic patients has gastroesophageal reflux disease (GERD) and 5-10% has peptic ulcer disease (PUD) (12). In the majority (50-70%) of patients no organic explanation is found after diagnostic work-up (functional dyspepsia)(12). Only 3 to 8% of all individuals with dyspeptic complaints consult their general practitioner(13-15). In follow-up 10 to 20% of the consulting patients is referred for endoscopy (15) The remaining patients are referred to as “uninvestigated dyspepsia”.
Acid inhibiting pharmacotherapy is the first choice treatment for dyspepsia (6)
It is demonstrated to be very effective in case of acid related symptoms such as in GERD (14;16). In patients with uninvestigated and functional dyspepsia the effectiveness of acid inhibitory drugs is lower (17;18).
No matter which acid inhibitory drug is used as initial treatment strategy for uninvestigated dyspepsia, the success rate remains unsatisfactory. Age, type and severity of complaints, H.pylori infection, psychological factors and genetic factors have been suggested to influence antacid treatment response in dyspepsia (18). The possibility to predict a positive or negative treatment response on various antacid drug treatment strategies will contribute to a more cost-effective management and could support a tailor made treatment strategy advice for individual patients with dyspepsia.

We report the determinants of short term (4 weeks) success and long term (12 weeks) failure of treatment with antacids and PPI in patients with a new episode of uninvestigated dyspepsia in primary care.

Methods

Design

This analysis is part of the DIAMOND study, a prospective, multicenter, randomized trial performed in primary care comparing the effectiveness of two treatment strategies for uninvestigated dyspepsia: step-up (antacid-H2RA-PPI) versus step-down (PPI-H2RA-antacid).

The DIAMOND study (19) design has been described in detail elsewhere (20). The study has been approved by the Medical Ethics Committee of the University Medical Centres Utrecht, Maastricht and Nijmegen.

Recruitment

Between October 2003 and January 2006, patients presenting with dyspepsia were recruited at 127 primary care centres in the southern and central part of the Netherlands. Patients were found eligible for the study if they had a new episode of dyspepsia, were 18 years or older and were able to fill out the Dutch questionnaires.

Patients were excluded if they used prescribed acid suppressive medication in the three months prior to consultation, had upper GI endoscopy in the year before inclusion, were diagnosed with malignancy of GI tract, had a contraindication to the study medication, were pregnant or had alarm symptoms (e.g. weight loss, bleeding or disturbed food passage).

Measurements

A self-administered postal questionnaire was used for assessment of demographic data: age (years), gender, height (m), weight (kg), marital status, level of education, working situation, as well as life style factors (consumption of alcohol, coffee, and smoking status) alcohol consumption, coffee consumption and smoking status were recorded as current users (yes/no). Body mass index (BMI) was calculated from self reported weight and height kg/(m²). Overweight was defined as BMI>25.

Two samples of venous blood were drawn. One sample was used to determine Helicobacter pylori antibodies (IgG) in serum (Pylori set EIA-G III; Orion Diagnostica Finland). A titer of more than > 20 units/ml was considered as a threshold for infection. The other sample was used to extract genomic DNA using the QIAamp DNA blood minikit (Qiagen, Hilden, Germany). Genotyping of the HTR3A C178T polymorphism (rs1062613) was performed by Molecular Beacon assay using the iCycler iQ real-time PCR detection system (BioRad, Hercules, CA, USA)

The dyspeptic symptoms were classified with a validated symptom questionnaire, (21) covering eight essential dyspeptic symptoms on a 7 point Likert scale. The symptom severity score, representing the sum of all items, ranges from 0-48, with higher scores indicating higher severity.

Psychopathology was measured using the Dutch version of the Symptom Check List-90 (SCL 90), which is a self-reporting, validated instrument with 90 questions, measuring 9 dimensions of psychological distress and psychopathology on a 5 point Likert scale. (22)

For measuring major life events (MLE) we used a modified version of Social Readjustment Rating Scale (SRRS) (23), comprising of 38 life events listed from most stressful to less stressful. We subcategorized the first 19 items as "highly stressful" events and items 20-38 as "stressful" events.

Coping styles were measured by a short version of the Utrecht Coping Questionnaire, which consists of 17 items. (24) Six coping styles (active coping, seeking support, avoidance coping, palliative coping, religious coping and passive reaction) are rated on a four-point Likert scale. Higher scores indicate that the specific coping style is more often adopted.

Pill count was used as a proxy indicator for medication compliance. Patients were classified as compliant if they used 80%-100% of medication.

Outcome

Short term treatment success was defined as adequate symptom relief after four weeks of treatment with either antacid or PPI, without further requirement of medication. Long term treatment failure was defined as no response to any of the study medication after 3 months.

Data analysis

All statistical analyses were performed with SPSS for Windows, version 14.0

Means and standard deviations (SD) were computed for continuous variables and medians and inter quartile range (IQ range) for continuous variables with skewed distribution. To test differences in socio-demographic factors, dyspepsia symptom severity, psychopathology, coping styles, major life events, and compliance between success and failure treatment subgroups parametric and non-parametric statistical tests were used when appropriate (Student's t-test, Mann Whitney U-test and X^2-test).

We used univariate and multivariate logistic regression analysis to determine risk factors associated with successful one month treatment with antacids as well as PPI. In addition we analysed factors associated with non response to any antacid drug

treatment after 3 months. All factors univariately associated with treatment success at $p \leq 0.25$ as well as biologically plausible factors (age and gender) were included in a backward logistic regression model to find those that were independently associated with either treatment success after one month, or treatment failure after three months. OR's with 95% confidence intervals (95% CI) were calculated. A receiver operating characteristics curve (ROC) was constructed to evaluate accuracy of model prediction. From variables who were independently associated with treatment success after one month, or treatment failure after three months, we constructed an ROC curve with the calculated probability of the event for each individual patient.

To retain power and precision as well as to prevent bias from missing values in a selective group of patients a single imputation procedure in SPSS version 14.0 was used. We imputed missing values (due to full or partially non response) for a range of 4%-15% of the questions of the SCL-90, gastrointestinal symptom questionnaire, UCL and MLE.

Results

Patient characteristics

A total of 664 patients participated in the DIAMOND-study. Of those, 11 patients did not use any study medication. Thus, data of 653 patients randomized to either the step-up (n= 334) or the step-down (n= 319) treatment arm were analysed. There were no differences between patients in the two treatment arms at baseline.

Successful treatment after 1 month

Table 1 shows the characteristics of patients with success and failure after one month of treatment with either antacids or PPI (the first step of the step-up respectively the step-down treatment strategy). In total 39.5 % (132/334) of the patients starting with antacid (step-up) treatment had adequate symptom relief after 1 month compared to 46.7% (149/319) (p=0,07) of the patients starting with PPI treatment (step-down). Patient characteristics that were univariately associated ($p \leq 0.25$) with successful antacid treatment were: epigastric pain, heartburn, regurgitation, nausea, halitosis and bloating, presence of symptoms of depression and somatisation and the application of a passive reaction coping style by the patients. A history of psychological problems in past 5 years was positively associated with treatment success (0.02) (table 2). In the multivariate analysis the presence of epigastric pain (OR 0.67; 95%CI: 0.67-0.94), heartburn (OR 0.88;

95%CI: 0.76-1), halitosis (OR 0.79 95%CI: 0.66-0.94) and a passive reaction coping style (OR 0.45; 95%CI: 0.45-0.88) made it less likely to become symptom free with antacids, while a history of psychological problems in the past 5 years (OR 2.3; 95% CI: 1.25-4.2) was found relatively more in patients being cured after one month treatment with antacids (table 3). The ROC area (AUC) of the model predicting treatment success on antacid (figure 1) based on these items was 0.67 (95% CI: 0.61-0.73).

Figure 1. ROC curve from multivariate logistic regression analysis of determinants of antacid treatment success

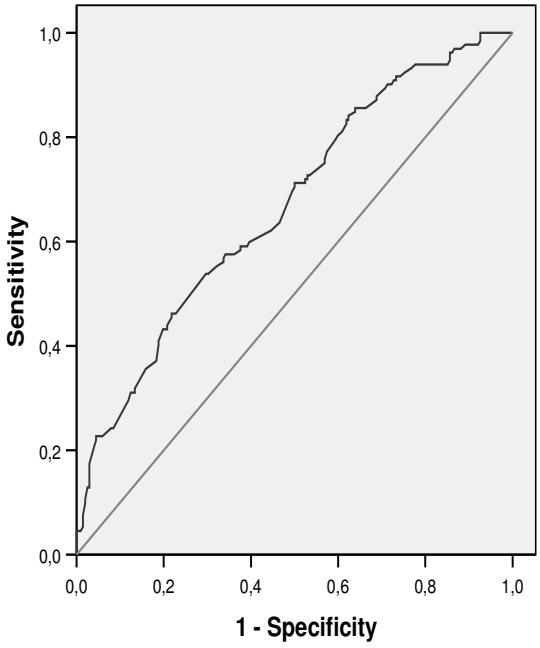


Table 1: Patients characteristics according to treatment outcome after step 1 of step-up and step-down treatment arm

		Antacid (Step-up) Treatment success				PPI (Step-down) Treatment success			
		Yes	sd	No	sd	Yes	sd	No	sd
Number of patients		132		202	sd	149		170	
Gender	Male n (%)	62 (47)		90 (44.6)		73 (49)		73 (42.9)	
	Female n (%)	70 (53)		112 (55.4)		76 (51)		97 (57.1)	
Age (years)	Mean sd	46.6	15.2	47		46.6	15.8	47.8	13.7
Education	0=no; 7=academic	3.6	1.8	3.6	13.9	3.7	1.8	3.7	1.7
Ethnicity	Caucasian n (%)	123 (93)		188 (93)	1.9	139 (93)		165 (97)	
	Other n (%)	9 (6.8)		14 (6.9)		10 (6.7)		5 (2.9)	
Marital status	Married living together (%)	96 (73)		150 (74)		114 (76.5)		135 (79.4)	
Working situation	Employed n (%)	87 (66)		130 (64)		93 (62.4)		98 (57.6)	
Smoking	Current n (%)	38 (29)		60 (30)		35 (23.5)		48 (28.2)	
Alcohol intake	Current n (%)	92 (70)		140 (69)		113 (75.8)		133 (78.2)	
HP serology	Seropositive n (%)	46 (35)		75 (37)		52 (34.9)		52 (30.6)	
Dyspepetic symptoms mean (sd)		14.96*	6.3	17.95		15.7*	6.4	17.5	6.5
Epigastric pain mean (sd)		2.07*	1.39	2.5	6.76	2.09*	1.4	2.46	1.18
Heartburn mean (sd)		2.3***	1.5	2.6	1.4	2.52	1.7	2.52	1.6
Regurgitation mean (sd)		2.0 **	1.4	2.39	1.63	2.21	1.6	2.32	1.4
Nausea mean (sd)		1.16***	1.4	1.46	1.6	1.4	1.4	1.5	1.4
Bloating mean (sd)		2.2*	1.48	2.68	1.5	2.15*	1.5	2.57	1.5
Belching mean (sd)		2.2	1.4	2.41	1.56	2.3***	1.5	2.49	1.5
Flatulence mean (sd)		2.21	1.36	2.34	1.56	2.1***	1.26	2.45	1.4
Halitosis mean (sd)		0.9*	1.16	1.48	1.39	0.96**	1.18	1.27	1.3
Reflux symptoms mean (sd)		6.4	1.6	6.6	1.65	6.6	2.3	6.6	1.9
HTR3a Genotype									
C/C allele's n(%)		67 (59)		124 (63)	1.9	78 (55.3)		111 (67.7)	
T/C & T/T allele's n(%)		47 (41)		73 (37)		63 (44.7)**		53 (32.3)	
History of Psych. Problems (%)		32 (24.2)**		28 (13.9)		41 (24.1)***		28 (18.8)	
SCL-90 scales:									
Agoraphobia mean (sd)		7.9	1.6	8.2		8	2.16	7.8	1.7
Anxiety mean (sd)		14.1	5.3	14.3	2.8	13.4 ***	3.9	14	4.6
Depression mean (sd)		23.0***	7.4	24.3	5.2	24.6	9.6	25	9.6
Somatisation mean (sd)		20.6**	6.4	22.3	8.7	20.5 ***	6.3	21.8	6.4
Obsessive-compulsive mean (sd)		13.9	5.1	14.6	7.5	14	5.2	14.4	5.3
Interpersonal sensitivity mean		24.6	9.8	24.8	5.8	25.1	9.7	24.5	9.3

(sd)									
Hostility mean (sd)		7.4	2.1	7.6	8.6	7.6	2.5	7.8	2.7
Sleeping problems mean (sd)		5.5	2.4	5.7	2.4	5.5	2.9	5.7	2.9
Psycho neuroticism mean (sd)		127.8 ***	38	133.6	3.0	128	34.5	131.9	36.6
Coping style					40				
Active coping mean (sd)		13.40	2.8	13.70		13.26	3.0	13.4	
Avoidance coping mean (sd)		3.75	1.2	3.73	2.90	3.7	1.2	3.6	1.19
Seeking support mean (sd)		11.5	3.5	11.4	1.24	10.9	3.0	10.9	3.16
Palliative coping mean (sd)		4.50	1.18	4.45	3.1	4.6	1.27	4.35	1.15
Religious coping mean (sd)		3.13	1.14	3.11	1.30	3.1	1.3	3.0	1.2
Passive* reaction coping mean (sd)		1.86	0.72	2.1	1.2	2.1***	0.8	1.96	0.7
Mediaction intake*	<80%	105 (79.5)		186 (92)	0.7	132 88.6)		164(96.5)	
	>=80%	27 (20.5)		16 (8)		17 (11.4)		6 (3.5)	

Significant at *<0.01; **<0.05; ***<0.25 level

Potential determinants that were associated with successful one month of PPI treatment were: the presence of epigastric pain, bloating, flatulence and halitosis, symptoms of anxiety and somatisation as well as psychological problems in the past 5 years, palliative and passive reaction coping style and the presence of the HTR3A C178T polymorphism (table 4). In multivariate analysis PPI treatment success after one month was independently inversely associated with epigastric pain (OR 0.77; 95%CI: 0.64-0.92), and flatulence (OR 0.82; 95%CI: 0.68-0.98) at inclusion. Treatment success was relatively more often found among patients with the HTR3A 178T polymorphism (OR 1.7; 95%CI: 1.1-2.8) and those using a predominantly palliative coping style (OR 1.24; 95%CI: 1.02-1.5) (table 4). The AUC of the model predicting treatment success on PPI (figure 2) based on these items was 0.66 (95% CI: 0.59-0.72).

Treatment failure after 3 months

After 3 months of treatment with either the step-up or the step-down strategy 80% of the patients were treated satisfactory. Only 20% of the patients remained symptomatic after all 3 treatment steps. Table 2 shows the patients characteristics according to the treatment outcome after 3 months. Factors potentially associated with non-response to treatment ($p \leq 0.25$) were epigastric pain, heartburn, regurgitation, bloating, nausea, belching, anxiety the use of an active coping style, the use of a palliative coping style, an avoidance coping style and being employed (table 5).

In the multivariate analysis failure of acid inhibiting drug treatment was associated with nausea (OR 1.24; 95%CI 1.1-1.42) and while anxiety increased the probability of a treatment response (table 5). However, the AUC of the model predicting

treatment failure on acid inhibiting drugs based on anxiety and nausea was 0.59 (95% CI: 0.53-0.64).

Discussion

In this study we found that patients with epigastric pain have a reduced chance of having adequate symptom relief on a short course (4 weeks) of both antacid and PPI treatment. Patients experiencing heartburn and halitosis are less likely to benefit from a short course treatment with antacids, while those experiencing flatulence are less likely to benefit from PPI. Patients with nausea are prone to fail on either acid inhibiting treatment, even after 3 months. However, considering the ROC-analysis, all differences found in our study were small.
The impact of psychological factors on antacid treatment outcome is more complex: patients with a history of psychological problems are more likely to have symptom

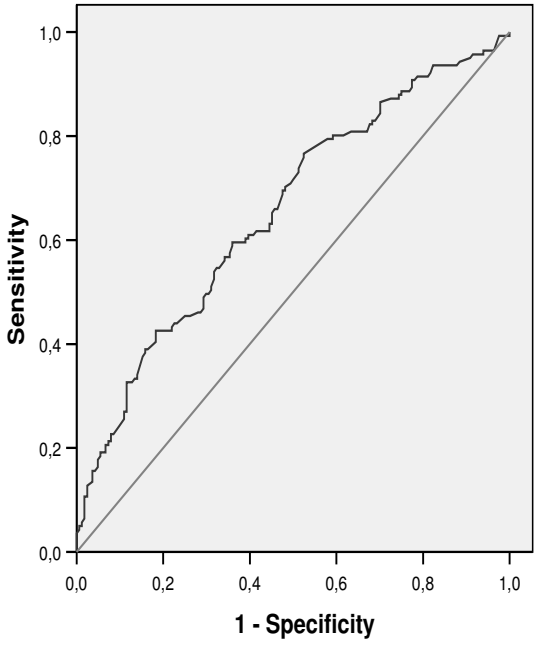
relief on 4 weeks of antacids, while those with present anxiety are less likely to have treatment failure after 3 months. Patients with a more palliative coping style have a higher likelihood of success on a short course of PPI treatment, while those with a passive coping style experience less effect of 4 weeks antacid treatment. Finally, success of short term PPI treatment was associated with the presence of the HTR3A 178T allele.
In the patient group that started with PPI as initial treatment especially non-reflux symptoms (pain and flatulence) were associated with poor treatment outcome after 4 weeks. Epigastric pain may require another approach (H.pylori test and treat or NSAID protection) and longer duration of treatment. Flatulence again is considered indicative of functional abdominal disease (27) such as NUD or IBS, which generally does not respond well to antacid treatment.

Table 2: Patients characteristics according to treatment outcome after 3 months of treatment

		Treatment outcome after 3 months			
		Success	sd	Failure	sd
Number of patients		523		130	
Gender	Male n (%)	233 (44.6)		65 (50)	
	Female n (%)	290 (55.4)		65 (50)	
Age (years)	Mean sd	46.8	14.9	47.9	13.2
Education	0=no; 7=academic	3.6	1.8	3.7	1.7
Ethnicity	Caucasian n (%)	490 (94)		125 (96)	
	Other n (%)	33 (6)		5 (4)	
Marital status	Married living together (%)	391 (75)		104 (80)	
Working situation	Employed n (%)	334 (64)***		74 (57)	
Smoking	Current n (%)	142 (27)		39 (30)	
Alcohol intake	Current n (%)	385 (73.6)		93 (71.5)	
HP serology	Seropositive n (%)	181 (34.6)		44 (33.8)	
Dyspepetic symptoms mean (sd)		16.4*	6.6	18.2	6.7
Epigastric pain mean (sd)		2.27***	1.37	2.45	1.32
Heartburn mean (sd)		2.45***	1.6	2.71	1.6
Regurgitation mean (sd)		2.20***	1.5	2.48	1.5
Nausea mean (sd)		1.33**	1.4	1.66	1.57
Bloating mean (sd)		2.4***	1.53	2.6	1.55
Belching mean (sd)		2.3**	1.5	2.63	1.47
Flatulence mean (sd)		2.27	1.37	2.4	1.33
Halitosis mean (sd)		1.17	1.35	1.29	1.6
Reflux symptoms mean (sd)		6.4	2	6.8	1.9
HTR3a Genotype					
C/C allele's n(%)		297 (60.6)		83 (65.9)	
T/C & T/T allele's n(%)		193 (39.4)		43 (34.1)	
History of Psych. Problems n(%)		105 (20.1)		24 (18.5)	
SCL-90 scales:					
Agoraphobia mean (sd)		8.0	2.2	7.9	2.1
Anxiety mean (sd)		14.1***	4.9	13.5	4.3
Depression mean (sd)		24.3	9.0	24.2	8.5
Somatisation mean (sd)		21.4	6.8	21.6	6.6
Obsessive-compulsive mean (sd)		14.3	5.4	14.1	5.3
Interpersonal sensitivity mean (sd)		24.9	9.6	24.1	7.9
Hostility mean (sd)		7.6	2.4	7.6	2.5
Sleeping problems mean (sd)		5.6	2.7	5.8	3.2
Psycho neuroticism mean (sd)		131	38	130	35
Coping style					
Active coping mean (sd)		13.4***	2.9	13.8	2.8
Avoidance coping mean (sd)		3.7***	1.2	3.6	1.2
Seeking support mean (sd)		11.2	3.2	11.3	3.1
Palliative coping mean (sd)		4.5***	1.2	4.3	1.3
Religious coping mean (sd)		3.1	1.2	3.1	1.2
Passive reaction coping mean (sd)		2.0	0.7	2.0	0.7

Significant at *<0.01; **<0.05; ***<0.25 level

Figure 2. ROC curve from multivariate logistic regression analysis of determinants of PPI treatment success



Patients with symptoms of nausea, which is supposed to be one of the key symptoms of functional dyspepsia, did not benefit from any acid inhibiting treatment strategy even after 3 months. Probably, the causal mechanism of the dyspeptic complaints in these patients is less likely to be acid related. In line with a previous study (25) we found a positive association between a history of psychological problems and a favourable response to relatively mild antacid treatment in case of dyspepsia. Individuals suffering from active psychological distress react with temporarily enhanced acid production, which probably results in experiencing dyspeptic symptoms (26).

Patients with predominant reflux symptoms (heartburn and to ea lesser extend regurgitation) were less likely to have adequate symptom relief with antacids. This again, agrees with previously reported findings of antacid drugs having the lowest success rate in GERD.(17)

The presence of the HTR3A 178T allele was associated with an increased rate of treatment success on PPI's. Serotonin 3 receptors are involved in mediation of visceral (hyper) sensitivity (peripherally) and an antinociceptive pathway centrally. The T allele is associated with altered receptor structure and as a consequence with a receptor which is less sensitive to serotonin (28-30). This in turn negatively affects signal transduction and consequently elevated perception of pain or other dyspeptic symptoms. If in a subset of patients, hypersensitivity to gastric acid is a cause of dyspeptic complaints strong acid inhibition by PPI could explain treatment success.
In this study we found that symptoms of nausea, flatulence (and belching) which were previously labelled as dysmotility like symptoms were negatively associated with successful acid inhibitory treatment. It has been previously reported that dysmotility symptoms do not improve on acid inhibition (31;32) and that prokinetics probably may be a better treatment option in this kind of patients.
Ideally treatment should correct the underlying pathophysiological mechanism. To date it has been difficult to identify this mechanism on dyspeptic symptoms only. Attempts were made earlier to categorize patients as reflux-like, ulcer-like or dysmotility like dyspepsia in order to treat them with appropriate medication. However, overlapping symptomatology (33) and change of symptom characteristics (34) and severity over time seem to withhold doctors from using symptom patterns in directing different treatment options.
In conclusion, our findings suggest that dyspeptic symptom patterns may predict treatment success with different acid inhibitor treatment strategy options. However, the magnitude of the associations was weak and do not allow firm recommendations for clinical practice. More knowledge is needed to tailor intervention strategies for these patients with confidence.

Table 3: Determinants of successful one month treatment with antacid (crude and adjusted OR, 95% CI)

	Crude OR† (n=477)	95 % CI	Adjusted OR¥	95% CI	p-value
Age	0.99	0.98-1.01			
Gender	1.10	0.70-1.70			
Epigastric pain	0.80	0.70-0.94	0.79	0.67-0.94	<0.05
Heartburn	0.88	0.77-1.01	0.88	0.76-1.00	0.07
Regurgitation	0.85	0.74-0.99			
Bloating	0.80	0.70-0.94			
Nausea	0.87	0.74-1.01			
Halitosis	0.75	0.64-0.89	0.79	0.67-0.94	<0.05
Depression	0.98	0.95-1.01			
Somatisation	0.97	0.94-0.99			
History of Psychological problems	2.00	1.13-3.50	2.3	1.25-4.20	<0.05
Passive coping	0.60	0.45-0.85	0.6	0.45-0.88	<0.05

† OR's and CI for the factors univariately associated with success after 1 months (p<=0.25)
¥OR's of factors independently associated with success after 1 months (p<0.05)

Table 4: Determinants of successful one month treatment with PPI (crude and adjusted OR, 95% CI)

	Crude OR†	95 % CI	Adjusted OR¥	95% CI	p-value
Age	0.99	0.98-1.01			
Gender	1.3	0.80-2.00			
Epigastric pain	0.80	0.70-0.95	0.77	0.64-0.92	<0.05
Bloating	0.80	0.70-0.96			
Belching	0.96	0.83-1.10			
Flatulence	0.80	0.70-0.97	0.82	0.68-0.98	<0.05
Halitosis	0.80	0.70-0.98			
History of Psychological problems	0.73	0.42-1.25			
Anxiety	0.96	0.92-1.02			
Somatisation	0.97	0.93-1.00			
Passive coping	1.24	0.92-1.70			
Palliative coping	1.16	0.96-1.40	1.24	1.02-1.50	<0.05
5 HTR3 178T allele	1.70	1.06-2.70	1.70	1.10-2.80	<0.05

† OR's and CI for the factors univariately associated with success after 1 months (p<=0.25)
¥ OR's of factors independently associated with success after 1 months (p<0.05)

Table 5: Determinants of treatment failure at 3 months (crude and adjusted OR, 95% CI)

	Crude OR†	95 % CI	Adjusted OR¥	95% CI	p-value
Age	1.01	0.99-1.02			
Gender	1.25	0.85-1.80	1.49	0.99-2.25	0.056
Employed	0.75	0.50-1.10	0.68	0.45-1.02	0.059
Heartburn	1.10	0.98-1.25			
Regurgitation	1.12	0.99-1.27			
Bloating	1.10	0.96-1.30			
Nausea	1.16	1.02-1.32	1.23	1.07-1.42	0.004
Belching	1.16	1.02-1.30	1.12	0.99-1.28	0.082
Anxiety	0.97	0.93-1.01	0.95	0.91-0.99	0.045
Palliative coping	0.90	0.60-1.50			
Avoidance coping	0.90	0.77-1.06			
Active coping	1.05	0.98-1.12			

† OR's and CI for the factors univariately associated with failure after 3 months ($p<=0.25$)

¥ OR's of factors independently associated with failure after 3 months ($p<0.05$)

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Chapter 8

General discussion

Suhreta Mujakovic

Introduction

In the papers presented in this thesis we report our studies on the influence of psychological state, major life events, coping style and genetic factors on dyspeptic symptom severity and the extend to which these factors affect the outcome of acid inhibiting treatment in primary care patients with dyspepsia. In the first section of this final chapter the main results are summarized. Then, the relation between psychosocial and psychiatric co-morbidity and dyspepsia will be discussed in a broader perspective. Genetic predisposition to the development of dyspepsia and the implications/ contributions of these findings for clinical practice will be outlined. Finally the consequences for clinical practice and recommendations for future research will be presented.

Main findings of this thesis

- Summarized evidence from systematically reviewed studies addressing the association between psychological problems (e.g. anxiety, depression and somatisation), personality disorders (e.g. neuroticism), major life events and coping style with dyspepsia pointed out that dyspeptic patients have elevated levels of personality and psychological disorders. Patients with dyspepsia appear to experience more major life events as compared to the healthy population, but there is no typical coping style which applies to all of them.
- In a cross sectional study in a population of patients with uninvestigated dyspepsia in primary care, we confirmed the association between dyspeptic symptom severity and psychopathology. Although this association was weak there appears to be a dose response relation between the extent of psychopathology and the severity of dyspeptic symptoms that patients experience. More than those with minor symptoms, patients with severe dyspepsia use an active coping style in an attempt to deal with the condition, for example by consulting their GP.
- The CYP2C19*2 genotype is associated with better outcme of PPI treatment, but is not a factor to be concerned in daily management of dyspepsia.
- From the selected genes of the serotonergic system (influencing symptom perception in the gastro-intestinal tract) only the serotonin HTR3A receptor

C178T polymorphism is likely to play a role in the intensity of dyspeptic symptoms.

- In primary care patients with uninvestigated dyspepsia a treatment strategy starting with PPI is equally effective as a strategy starting with antacids.
- We found epigastric pain, heartburn, halitosis and a passive coping style to withhold patients from succesfull one month treatment with antacids. Psychological problems in the past five years were associated with treatment success with antacids after one month. Epigastric pain and flatulence were found to withhold from PPI treatment success, while the presence of HTR3A 178T polymorphism and the use of a palliative coping style were positively associated with PPI treatment success. Treatment failure in all strategies after 3 months was relatively common in males and in patients with dysmotility symptoms such as bloating and nausea.

Psychopathology, in dyspepsia; causal factor or co-morbidity

To date there is no evidence for a causal relation between psychopathology and dyspeptic symptoms. Results from our meta-analysis (chapter two) suggest that in dyspeptic patients the levels of psychological and personality disturbances are elevated, but there is ample uncertainty about the magnitude of the association and the impact of this relation because of the large heterogeneity of the available studies.
In the cross-sectional study (chapter three) the prevalence of psychiatric disease in patients with uninvestigated dyspepsia was 20% over the past five years and 10% at the time of inclusion, which was similar to the general population (1) This suggests that confirmed psychiatric morbidity is not a major factor in the presentation of dyspepsia in the unselected primary care patient group. However, in this study we demonstrated that early symptoms of psychopathology, measured psychometrically with a self-administered questionnaire, were associated with dyspeptic symptom intensity. Especially symptoms of somatisation and mood disorders were more common among patients with more severe dyspepsia. In the absence of confirmed clinical psychiatric diagnoses, increased levels of anxiety, depression and somatisation may indicate increased levels of psychological distress. This might contribute to the aetiology of dyspeptic symptoms. .
We studied a population with uninvestigated dyspepsia, which harbors both patients with organic disease (GORD and PUD) and patients with functional dyspepsia. In the latter group no organic cause is found for the dyspeptic symptoms and many consider this group as particularly subject to other etiological factors such as

psychological disturbance. However, there is hardly any evidence in the literature that these patients indeed have more psychosocial co morbidity. Instead it appears that there is no difference between patients with organic dyspepsia (e.g. reflux) and functional dyspepsia regarding personality and psychological disturbances Therefore, even though functional dyspepsia might have been overrepresented in our study population, we do not think this has biased the association with psychopathology.

Major life events are also considered to play a role in the development and exacerbation of dyspeptic symptoms through acute or chronic exposure to distress (2)
Even though the findings in our meta- analysis suggests that all major life events are a risk factor for dyspepsia, in our cross sectional study we could only confirm this association for severe MLE (e.g. death of a family member) (chapter 3). This could mean that the causal role of an MLE in the generation of dyspeptic symptoms depends on the perceived severity of the stress it generates. How each individual will react on the stressor (=MLE) is actually depending on the coping style applied to deal with it. In our study (chapter 4) we found that patients with severe symptoms are more likely to deal actively with a health problem (dyspepsia). This contrasts with the opinion that dyspeptic patients tend to have a passive health care behaviour. In the literature there is no agreement about which coping style is most effective or desirable. In the trial we found a passive coping style to be associated with treatment failure on antacids after one month and treatment success with PPI's after one month. Although this is an interesting finding, suggesting that patients with a passive coping style might be helped better with strong medication; we conclude that the preferred coping style of the individual patient is not an easily measurable issue to be considered in treatment choices for dyspepsia
In conclusion, there remains significant uncertainty about the role of psychopathology in dyspepsia. Based on our results we hypothesize that psychological distress, in some cases caused by severe major life events, contributes to increased anxiety and depression on the one hand and to an increased sensitivity to physical symptoms on the other. Both mechanisms make patients more susceptible to experience dyspeptic symptoms, especially those patients who tend to somatize. Coping mechanisms have a problem solving role but mainly determine healthcare seeking behaviour.

Dyspepsia and genes; is there a genetic vulnerability for dyspepsia?

From a pathophysiological perspective the CYP2C19*2 genotype is a major factor in the PPI metabolism. Polymorphism in the gene results in delayed PPI metabolisation, resulting in prolonged half time and consequently prolonged acid inhibition. In theory this would mean that patients with the CYP2C19*2 allele will have the greatest benefit from PPI treatment, and that the PPI dose in slow metabolizing patients could possibly be adjusted; with a minority of the patients requiring a lower dosage of PPI. This hypothesis was supported by study (3) that demonstrated that cure rates of GORD were higher in patients homozygous for CYP2C19*2 genotype. However, in detailed analysis of the PPI treatment result in relation to the genetic profile (chapter 5) we detected a significant symptom reduction in patients with CYP2C19*2 genotype. However, due to low prevalence of homozygous carriers of CYP2C19*2 allele, the CYP polymorphism does not have major consequences for PPI treatment in daily clinical practice.

The neurotransmitter serotonin is considered to be an important mediator in the brain gut axis, and suggested to be contributing to the generation of gastro-intestinal symptoms (4;5).

Thus, polymorphisms in the genes involved in the serotonin signalling pathway may play a role in dyspepsia. In our analysis (chapter 6) we could confirm this role for the HTR3A gene, but not for serotonin re-uptake transporter gene. We found an association of functional polymorphism C178T in serotonin receptor HTR3A with severe dyspeptic symptoms. The mechanism underlying this association is probably through an anti-nociceptive pathway in which HT3 receptors play important role (see chapter 6 for details). No direct association for the serotonin reuptake transporter gene was found when considered as a single factor. However, homozygosity for the long/long SERT genotype in combination with HTR3A 178T polymorphism was demonstrated to increase the risk of severe dyspeptic symptoms. It is possible that a desensitized HT3a receptor (caused by 178T allele) in combination with rapid serotonin reuptake (caused by the l/l SERT genotype) results in rapid termination of the serotonin induced signalling, which results in reduced anti-nociception and enhanced risk for severe dyspeptic symptoms. It is not so surprisingly that no effect was found for SERT alone. Polymorphisms of SERT gene influence the serotonin reuptake and through that the availability of serotonin at the receptor. From studies in animal models it is known that the receptor changes its properties depending on serotonin availability, thereby becoming (more or) less sensitive (6).

In our study on cost effectiveness of antacid treatment strategies (chapter 7) no difference was detected between a step-up and step-down treatment strategy. This supports the current Dutch multidisciplinary dyspepsia guideline, which recommends a step-up treatment regime for all patients with non–alarming dyspeptic symptoms, starting with antacids or H-2 blocking agents, and reserving PPI treatment for those patients with persisting complaints (7) In addition our results also support the recommended time frame chosen in the multidisciplinary guideline. Short term treatment appears to be effective in 40%-47% of the patients (chapter 8). After three months of treatment, about 80 % of the patients benefits from the acid inhibiting treatment strategy. This demonstrates that the 2 months time window which is recommended for the first phase of treatment with antacids, before starting with PPI treatment, is probably the most cost effective approach in dyspepsia management

A small percentage of dyspeptic patients will not respond to any antacid medication. Although in our study dysmotility like symptoms as belching and nausea at the beginning of treatment are associated with failure at three months, it seems difficult to distinguish this group using symptoms only (chapter 9).

Implications of this thesis for clinical practice and future research

Despite the associations we identified, psychological and genetic factors have no direct consequences for the clinical dyspepsia management of the majority of dyspeptic patients in primary care. The type and the intensity of dyspeptic symptoms are the main factors directing the treatment of dyspepsia. As we found no difference between initial PPI and initial antacid treatment, there is no reason to change the current Dutch guidelines for management of dyspepsia: start with antacids for a period of one to two months before stepping up to PPI treatment. .

For about 20 % of the patients the results of long term acid inhibiting treatment remains unsatisfactory. Predominant symptoms of dysmotility (nausea and belching) could at least partly explain treatment failure. These symptoms might better be treated with prokinetic drugs (7). In addition, in patients who fail on antacid treatment psychological factors should be explored. Treatment with either psychological interventions or antidepressants might be a more effective treatment option in the subset of patients with serious psychopathology although evidence from properly conducted randomized trials is still lacking. In the future, genes of serotonergic system may offer a potential target for novel drug treatment of severe dyspepsia. However, more research on the role of serotonin receptors in the

aetiology and severity of dyspepsia symptoms is needed to establish the role of the serotonergic system in the generation of dyspeptic symptoms.

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Summary

Dyspepsia is a very common condition in the population, accounting for 3-8 % of all primary care consultations. The complex multifactorial aetiology of this syndrome, which involves stomach hyperacidity, dysmotility, psychosocial co-morbidity and genetic predisposition, makes it difficult to establish a uniform strategy for initial management of dyspepsia. Moreover, frequent therapeutic failure, easy symptom relapse and a high placebo response add to the problems in identifying the optimal primary therapeutic approach for each individual patient. The choice of the initial treatment is basically guided by the presented symptoms In addition other patient characteristics, such as demographic factors, psychosocial background, Helicobacter infection and genetic factors are suggested to determine success of dyspeptic treatment, but their exact contribution is unknown.

The background and rationale for this thesis are outlined in chapter one. The main goal of our studies was to investigate which psychosocial, personality and genetic factors might affect dyspeptic symptom severity and determine the effectiveness of current treatment options.

In Chapter 2 we describe the results of a systematic review and meta-analysis of the association between psychosocial factors and dyspepsia. We compared outcomes of the studies investigating one or more of the following determinants: psychopathology, personality disturbances, major life events and coping ability in dyspeptic patients and healthy controls. The combined data from these studies showed an increased presence of psychiatric and personality disturbances in patients with dyspepsia. Moreover, there were marked differences in frequency of major life events and coping behaviour between dyspeptic patients and healthy controls. Although the results of these studies were very consistent the exact quantitative effect of personality and psychiatric factors on the aetiology of dyspepsia cannot be derived from this analysis. The main reason for this is the relatively poor quality of the studies, which does not allow a firm conclusion about their results. We concluded that more population based, well-designed prognostic studies addressing the relation between psychological factors and dyspeptic symptoms and treatment outcome are needed to be able to draw more detailed conclusions about the consequences of the presence of psychosocial factors for dyspepsia management in clinical practice.

In Chapter 3 we describe the relationship between psychopathology (measured psychometrically), coping style, major life events and dyspeptic symptom severity in 664 primary care patients with uninvestigated dyspepsia. We found that there is a direct linear relationship between dyspeptic symptom severity and psychopathology and coping style. In particular the presence of somatisation, depression, younger age and the use of an active coping style were found to be associated with severe dyspepsia.
Furthermore, we found that patients with mild dyspepsia do not differ from the general population in the terms of psychological profile. In contrast, patients with moderate and severe dyspepsia score higher than the average population on all dimensions of SCL90. These results did not alter when the patients with a historical or current psychiatric diagnosis were taken into account. We concluded that symptoms of depression and somatisation are associated with dyspepsia symptom severity in patients consulting with a new episode of dyspepsia. In addition to drug treatment, routine exploration of the psychopathological background of the patient should be recommended in the clinical management of severe dyspepsia.

In Chapter 4 we present the results of an analysis of the relative influence of the CYP2C19*2 genotype on treatment success in 319 patients starting with PPI as initial treatment for dyspepsia. The speed of the hepatic metabolism of PPI is dependent on the CYP (450) 2C19 enzyme. Genetic polymorphism in CYP2C19 creates slower metabolisation of proton pump inhibitors, which might have consequences for the PPI dosage.
The distribution of CYP2C19*2 genotype among the participating patients was: 71% rapid metabolizer (RM). 25.6% intermediate metabolizer (IM) and 3.4% poor metabolizer (PM). Treatment with PPI was successful in 70% of PM. 58.7% of IM and in 55.3 % of RM ($p > 0.05$). Symptom improvement, measured as the percentage of decrease in mean initial symptom score after 4 weeks, was 65.8% in PM. 48.7 % in IM group and 44.3% in RM group (Trend $p=0.02$).
In multivariate analysis PPI treatment outcome at 4 weeks was independently associated with baseline dyspeptic symptom severity (OR 0.94 95%CI:0. 90-0.97).
Our study confirms that CYP2C19*2 polymorphism causes slower PPI metabolisation and may be related to increased treatment efficacy in PPI treatment. However, since the prevalence of PM is very low, the genetic status does not seem to have major impact on the treatment of uninvestigated dyspepsia in daily clinical

care. The severity of dyspeptic symptoms appears to be most predictive for PPI treatment success.

In Chapter 5 we describe the association study between functional polymorphisms in serotonin receptor HTR3a (C187T), 44 bp insertion/deletion polymorphism in serotonin reuptake transporter (SERT) and dyspeptic symptoms (severity). HTR3A C178T allele carriers were more prevalent in patients with severe dyspepsia (odds ratio (OR) 1.5; 95% CI 1.05-2.10). This association appeared to be stronger in females (OR 1.9 (1.2-3.1)) than in males (OR 1.04 (0.6-1.8)) and stronger in patients homozygous for the insertion/insertion SERT-P genotype (OR 2.05 (1.07-3.92). In females with insertion/insertion SERT-P genotype the association with dyspeptic symptoms was highest (OR 3.6 (1.5-8.6)).
The results of this study suggest that patients who have HTR3A 178T polymorphism are at increased risk of having severe dyspeptic symptoms. We conclude that altered HTR 3a receptor function - alone or in combination with SERT-P genotype- could explain differences in dyspeptic symptom severity. However, further research is needed to clarify the clinical consequences of this finding.

In Chapter 6 we report on the outcome of the DIAMOND trial, and analyse the cost-effectiveness of two treatment strategies for uninvestigated dyspepsia. We demonstrated that a step-up strategy starting with antacids is more cost-effective than a step-down strategy starting with proton pump inhibitors in the initial management of dyspepsia in primary care. The step-up regimen resulted in slightly lower medical as well as overall costs with equal clinical effectiveness as compared to the step-down approach. Costs were primarily sensitive to prices of medication, minimizing the difference in costs between the strategies when prices of generic medication instead of specialities were regarded.
The step-up approach was more cost-effective at 6 months in patients with new onset dyspepsia than a step-down approach. Nonetheless, patients on initial empirical treatment with proton pump inhibitor (step-down) show an earlier response, especially in the subgroup with predominant reflux symptoms. These results support the strategy as proposed in the Dutch multidisciplinary guidelines for dyspepsia.

In Chapter 7 we present the results of the study on the determinants of successful short term treatment of dyspepsia with antacids and PPI Furthermore, determinants of long term therapy failure are described.
In this study we found that patients with epigastric pain have a reduced chance of having adequate symptom relief on a short course (4 weeks) with both antacids as well as PPI treatment. Patients experiencing heartburn and halitosis are less likely to benefit from a short course treatment with antacids, while those experiencing flatulence are less likely to benefit from PPI. Patients with nausea are prone to fail on either acid inhibiting treatment, even after 3 months.
Our findings suggest that dyspeptic symptom pattern may to a certain extent predict treatment success with different acid inhibitor treatment strategy options. However, the magnitude of the associations was limited and does not allow firm recommendations for clinical practice.

Finally, in Chapter 8 we synthesize the results from these studies, and discuss how psychopathology, coping style, major life events and genes influence the severity of dyspeptic symptoms and ultimately the outcome of acid inhibitory treatment.

Samenvatting

Dyspepsie is een veelvoorkomende aandoening die verantwoordelijk is voor 3-8 % van alle consulten in de eerstelijns gezondheidszorg. De complexe en multifactoriële etiologie van dit syndroom, waarin hyperaciditeit, dysmotiliteit, psychosociale comorbiditeit en genetische aanleg een rol spelen maakt het moeilijk om een uniforme initiële behandeling van maagklachten aan te bevelen. Inadequate reactie op medicamenteuze therapie, een snel recidief na staken, en een hoge placebo respons dragen bij aan de problemen rondom het vinden van de optimale initiële behandel strategie.
De behandelkeuze is primair gebaseerd op de gepresenteerde symptomatologie. Daarnaast blijken andere factoren, zoals de demografische en psychosociale achtergrond van de patiënt, Helicobacter infectie en genetische factoren een rol te spelen in het slagen van de behandeling, hoewel het niet duidelijk is wat hun exacte bijdrage is.

De achtergrond en de motivatie voor de studies beschreven in dit proefschrift worden uiteengezet in het eerste hoofdstuk. Het belangrijkste doel was om te onderzoeken welke psychosociale, persoonlijkheid en genetische factoren een rol spelen bij maagklachten en in welke mate zij de ernst van de klachten en effectiviteit van zuur remmende behandeling beïnvloeden.

In hoofdstuk 2 worden de resultaten van een systematische review en meta-analyses naar de relatie tussen psychosociale factoren en dyspepsie beschreven. Wij vergeleken de resultaten van onderzoeken naar de prevalentie van een aantal belangrijke psychosociale determinanten (psychopathologie, persoonlijkheid stoornissen, belangrijke levenservaringen en coping mechanismen) onder dyspeptische patiënten en gezonde controles. De gecombineerde data van deze studies lieten een toename zien van psychiatrische en persoonlijke stoornissen bij patiënten met dyspepsie in vergelijking tot gezonde personen. Ook werd een verschil aangetoond in het aantal negatieve levenservaringen en coping stijl. Hoewel de resultaten van de studies zeer consistent waren, kon de exacte bijdrage van de psychiatrische en persoonlijkheidsfactoren op de etiologie van dyspepsie op basis van deze analyses niet worden vastgesteld. De belangrijkste reden hiervoor was de beperkte methodologische kwaliteit van de studies. Wij concludeerden dat meer prognostische studies met gedegen methodologie nodig zijn om eenduidige

conclusies te kunnen trekken over de invloed van psychosociale factoren op dyspepsie en de uitkomst van behandeling.

In hoofdstuk 3 wordt de relatie beschreven tussen psychopathologie, copingstijl, levensgebeurtenissen en ernst van maagklachten bij 664 eerstelijns patiënten met niet-nader- onderzochte maagklachten. Er bleek een lineair verband te bestaan tussen de ernst van de dyspepsie enerzijds en psychopathologie en copingstijl anderzijds. Jongere leeftijd, de aanwezigheid van symptomen van somatisatie en depressie, en het gebruik van een actieve coping stijl bleken geassocieerd met ernstige dyspepsie.
Patiënten met milde symptomen van dyspepsie bleken wat betreft hun psychologische profiel niet af te wijken van de gezonde populatie. Daarentegen scoorden patiënten met matige tot ernstige dyspepsie hoger op alle dimensies van de SCL90 in vergelijking met de gezonde populatie. Wanneer we corrigeerden voor de aanwezigheid van een actuele psychiatrische diagnose, bleek dit geen invloed te hebben op de resultaten. Wij concludeerden dat onder patienten met een nieuwe episode van maagklachten symptomen van depressie en somatiseren geassocieerd zijn met ernst van dyspeptische klachten. Geadviseerd kan worden om naast het instellen van een medicamenteuze behandeling ook de psychopathologie van de patiënt te inventariseren en de uitkomst hiervan mee te laten wegen in de keuze van de behandeling.

In hoofdstuk 4 worden de resultaten gepresenteerd van het onderzoek naar de invloed van het CYP2C19*2 genotype op de behandeling van de dyspeptische patiënten met een protonpompremmer (PPI. De snelheid waarmee PPI in de lever gemetaboliseerd wordt, is afhankelijk van het CYP(450)2C19 enzym. Genetisch polymorfisme in CYP2C19 zorgt voor een langzamer metabolisme van protonpompremmers, wat mogelijk van invloed is op de PPI dosering.
De frequentie van het CYP2C19*2 genotype over de onderzoekspopulatie van 319 patienten die 4 weken met een PPI behandeld werden was als volgt: 71% van de patiënten had een snel metaboliserende genotype (RM), 25,6% een gemiddeld metabolisme (IM) en 3,4% een langzaam PPI metabolisme (PM). De behandeling met PPI was na 4 weken succesvol bij 55,3% van de RM, 58,7% van de IM en 70% van de PM ($p>0.05$). De verbetering van de symptomen, gemeten als percentage van afname in gemiddelde initiële symptomen score na 4 weken, was 65,8% voor PM, 48,7% in de IM groep en 44,3% in de RM groep (trend $p=0.02$).

Uit de multivariate analyse bleek dat de uitkomst van behandeling na 4 weken onafhankelijk geassocieerd was met de ernst van maagklachten bij aanvang van de studie (OR 0.94 95%CI:0.90-0.97).
Deze resultaten laten zien dat CYP2C19*2 polymorfisme door een vertraagd PPI metabolisme leidt tot een meer succesvolle PPI behandeling. Omdat de prevalentie van PM laag is, speelt de genetische achtergrond waarschijnlijk geen rol in de behandeling van dyspepsie in de dagelijkse praktijk. De ernst van de symptomen blijkt de beste voorspeller van behandelsucces met PPI.

In hoofdstuk 5 wordt een onderzoek beschreven naar de associatie tussen functionele polymorfismen in serotonine receptor HTR3a (C187T), 44bp insertie/deletie polymorfisme in serotonine re-uptake transporter (SERT) en dyspeptische symptomen. HTR3A 178T allel dragers kwamen meer voor bij patiënten met ernstige dyspepsie (odds ratio (OR) 1.5; 95% CI 1.05-2.10). Deze relatie bleek sterker onder vrouwen (OR 1.9 (1.2-3.1)) dan onder mannen (OR 1.04 (0.6-1.8)) en sterker bij patiënten die homozygoot waren voor het insertie/insertie SERT-P genotype (OR 2.05 (1.07-3.92). Onder vrouwen met het insertie/insertie SERT-P genotype was het verband met dyspeptische symptomen het sterkst (OR 3.6 (1.5-8.6)).
De resultaten van deze studie suggereren dat patiënten met HTR3A 178T polymorfisme een groter risico hebben op dyspeptische klachten. Geconcludeerd kan worden dat een veranderde serotonine receptor functie - alleen of in combinatie met het SERT-P genotype- voor een deel de ernst van de maagklachten kan verklaren. Vervolgonderzoek is nodig om de klinische betekenis van deze bevindingen vast te stellen.

In hoofdstuk 6 worden de resultaten van de DIAMOND trial weergegeven. De kosteneffectiviteit analyse van twee behandelstrategieën voor niet nader onderzochte maagklachten wordt gepresenteerd. Een zogenaamde step-up behandeling (gestart met antacidum 4weken, bij falen 4 weken H 2 RA, bij falen 4 weken PPI) bleek na 6 maanden kosten-effectiever dan een step-down benadering waarbij gestart wordt met protonpompremmers. De step-up behandeling leidde tot minder medische en minder algemene kosten dan de step-down behandeling, terwijl het klinisch effect hetzelfde was. De kosten zijn afhankelijk van de prijs van de medicamenten, waarbij de kosten gedrukt kunnen worden door het voorschrijven van generieke medicatie in plaats van de spécialités.

De step-up benadering blijkt na 6 maanden behandeling kosten-effectiever dan de step-down benadering. Niettemin bleek dat patiënten die behandeld werden met protonpompremmers (step-down benadering) eerder effectieve klachten reductie hadden, met name in de groep met overwegend reflux symptomen. Deze resultaten ondersteunen de primaire behandelstrategie zoals die wordt geadviseerd in de Nederlandse multidisciplinaire richtlijn Maagklachten

In hoofdstuk 7 worden de resultaten beschreven van de studie naar de determinanten van succesvolle 4 weekse behandeling met antacida dan wel met PPI . Tevens worden de determinanten van het falen van medicamenteuze behandeling op lange termijn beschreven.

Wij vonden dat patiënten met epigastrische pijn een kleinere kans hadden op behandelsucces met 4 weken antacidum of PPI behandeling. Patiënten met zuurbranden en halitosis bleken minder baat te hebben bij een primaire behandeling met antacida, terwijl patiënten met flatulentie minder baat hadden bij een behandeling met PPI. Patiënten met de klachten van misselijkheid reageerden onvoldoende op antacida dan wel PPI, zelfs na 3 maanden behandeling.
De resultaten suggereren dat het type dyspeptische klachten een rol speelt in het succes van de behandeling met maagzuurremmers. Echter, de beschreven associaties zijn zwak en nog niet te vertalen naar aanbevelingen voor het klinisch beleid bij dyspepsie

In hoofdstuk 8 zetten we de resultaten van de verschillende studies op een rij en bediscussiëren in welke mate psychopathologie, copingstijl, negatieve levenservaringen en genetische aanleg van invloed zijn op de ernst van de maagklachten en het resultaat van behandeling met maagzuurremmende medicatie beïnvloeden.

Publicaties en presentaties

Gepubliceerde abstracts

Mujakovic S, De Wit NJ, Van Marrewijk CJ, Fransen GAJ, Onnen-Moret NC, Laheij RJF, Muris JWM, Grobbee DE, Samsom M, Jansen JBMJ, Knottnerus JA, Ter Linde J, Numans ME. C178T Polymorphism in the 5HT3A receptor is associated with severity of dyspeptic symptoms. Gut suppl No III, vol 59, oktober 2007.

Mujakovic S, De Wit NJ, Van Marrewijk CJ, Fransen GAJ, Stijnenbosch P, Laheij RJF, Muris JWM, Grobbee DE, Samsom M, Jansen JBMJ, Knottnerus JA, Ter Linde J, Numans ME. CYP2C19*2 Polymorphism does not affect PPI treatment success in primary care patients with dyspepsia. Gut suppl No III, vol 59, oktober 2007.

Mujakovic S, De Wit NJ, Laheij RJF, Muris JW, Numans ME."Psychopathology in primary care patients with uninvestigated dyspepsia." GUT suppl No VII, vol 54, oktober 2005

Mujakovic S, De Wit NJ, Laheij RJF, Muris JW, Numans ME. "The relation beteween dyspepsia and psychiatric and psychosocial factors, a systematic review." GUT suppl No VII,vol 54, oktober 2005

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Jesse, mijn grote jongen, mama is eindelijk klaar met al dat werk achter de computer. Liefje dank je wel dat je braaf met mama wel eens uren in de auto zat onderweg om bloedmonstertjes op te halen en op het laatst samen met mama achter computer zat te "werken".
Maxje, jij bent je nog te klein om te begrijpen wat mama aan het doen is, maar ik ben reuze trots op jou.

Curriculum vitae

Suhreta Mujakovic is geboren op 26 juli 1973 in een klein Bosnisch stadje Derventa. In 1992 behaalde zij haar middelbare school diploma (vergelijkbaar met het Nederlandse VWO) en wilde graag Tandheelkunde studeren, maar wegens de oorlog in Bosnie mocht het niet zo zijn. Hetzelfde jaar nog verliet zij voorgoed Bosnie en zij woont sinds 1993 in Nederland. In 1996 begon zij met de HBO opleiding Verpleegkunde en studeerde af in 2000 op de GGD Zuid Limburg. Deze stage maakte zodanig indruk op haar dat zij besloot om verder te gaan studeren. In september 2000 begon zij met de studie Gezondheidswetenschappen en koos Biologische Gezondheidskunde als afstudeerrichting. Drie jaar later studeerde zij af, op de afdeling Humane Biologie, aan een project over medicamentuze behandeling van de obesitas.

Vanaf april 2003 tot en met december 2006 heeft zij gewerkt aan de Universiteit Utrecht, Divisie Julius Centrum voor Gezondheidswetenschappen en Eerstelijns Geneeskunde als junior onderzoeker aan het Diamond project. Tijdens deze periode heeft zij als onderdeel van haar promotie traject de opleiding “Genetic Epidemiology” aan het NIHES instituut te Rotterdam gevolgd en in 2006 haar diploma behaald.

Suhreta Mujakovic woont samen met Raoul Backus en zij hebben twee zoons Jesse en Maximé Backus.

Pragmatic trials in primary care: methodological challenges and solutions demonstrated by the DIAMOND-study

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BMC Med Res Meth 2007; 7: 16.

Abstract

Background: Pragmatic randomised controlled trials are often used in primary care to evaluate the effect of a treatment strategy. In these trials it is difficult to achieve both high internal validity and high generalisability. This article will discuss several methodological challenges in designing and conducting a pragmatic primary care based randomised controlled trial, based on our experiences in the DIAMOND-study and will discuss the rationale behind the choices we made. Future pragmatic trials may benefit from the successes as well as the problems we experienced.

Discussion: The first challenge concerned choosing the clinically most relevant interventions to compare and enable blinded comparison, since two interventions had very different appearances. By adding treatment steps to one treatment arm and adding placebo treatment to both treatment arms both internal and external validity were optimized. Nevertheless, although blinding is essential for a high internal validity, it should be warily considered in a pragmatic trial because it decreases external validity. Choosing and recruiting a representative selection of participants was the second challenge. We succeeded in retrieving a relatively large, representative patient sample by carefully choosing (few) inclusion and exclusion criteria, by random selection, by paying much attention to participant recruitment and taking the participant's reasons to participate into account. Good and regular contact with the GPs and patients was to our opinion essential. The third challenge was to choose the primary outcome, which needed to reflect effectiveness of the treatment in every day practice. We also designed our protocol to follow every day practice as much as possible, although standardized treatment is usually preferred in trials. The aim of this was our fourth challenge: to limit the number of protocol deviations and increase external validity.

Summary: It is challenging to design and conduct a pragmatic trial. Thanks to thorough preparation, we were able to collect highly valid data. To our opinion, a critical deliberation on forehand of where on the pragmatic-explanatory spectrum you want your trial to be, in combination with consulting publications especially on patient recruitment procedures, has been helpful in conducting a successful trial.

Introduction

Pragmatic trials are designed to investigate how effective a treatment strategy is in everyday practice.[1] The hypothesis and study design in pragmatic trials are developed specifically to answer questions of decision makers[2] and should compare new with existing interventions in the indicated population using relevant health outcomes.[3] Researchers face a number of methodological challenges and need to make several choices in the design and conduct of pragmatic trials. This is especially true for primary care based trials where the broad spectrum of disease presentation and early clinical stage challenges the selection of an adequate study population. Though these challenges greatly influence the external and internal validity as well as the eventual significance of the study results, most publications do not elaborate on the choices made. This paper discusses several challenges in designing and conducting pragmatic primary care based trials we experienced in a large scale multicentre randomised trial on dyspepsia. This might be helpful for other researchers especially in the planning stage of new trials. Our objective is to contribute to quality improvement of pragmatic primary care based trials.

This paper will discuss three challenges in designing a study: choosing the right intervention and blinding treatment allocation, choosing an appropriate study population, and choosing the essential outcome measures. Subsequently the challenges in conducting a study will be discussed focusing on recruitment of participating general practitioners (GPs) and patients, and on dealing with protocol deviations. Each section will start with a brief introduction of pitfalls in general, followed by the rationale behind the choices made within the DIAMOND-study and a speculation of the consequences of our choices. The paper will end with conclusions describing the consequences of our choices for the expected usefulness and relevance of the DIAMOND results.

The DIAMOND trial

The Dutch study of InitiAl Management Of Newly diagnosed Dyspepsia (DIAMOND) investigates the effectiveness of two treatment strategies for dyspepsia: the 'step-up' treatment strategy and the 'step-down' treatment. The 'step-up' treatment starts with antacids and, if the symptoms persist or recur, builds up to stronger medication, while the 'step-down' treatment starts with the strongest drug (proton pump inhibitor (PPI)) and reduces stepwise to H_2-Receptor Antagonists (H_2RAs) and antacids as long as the symptoms persist or recur. In Box 7.1-7.4 and

Figure 7.1-7.2 the design and research questions of the DIAMOND-study are described.

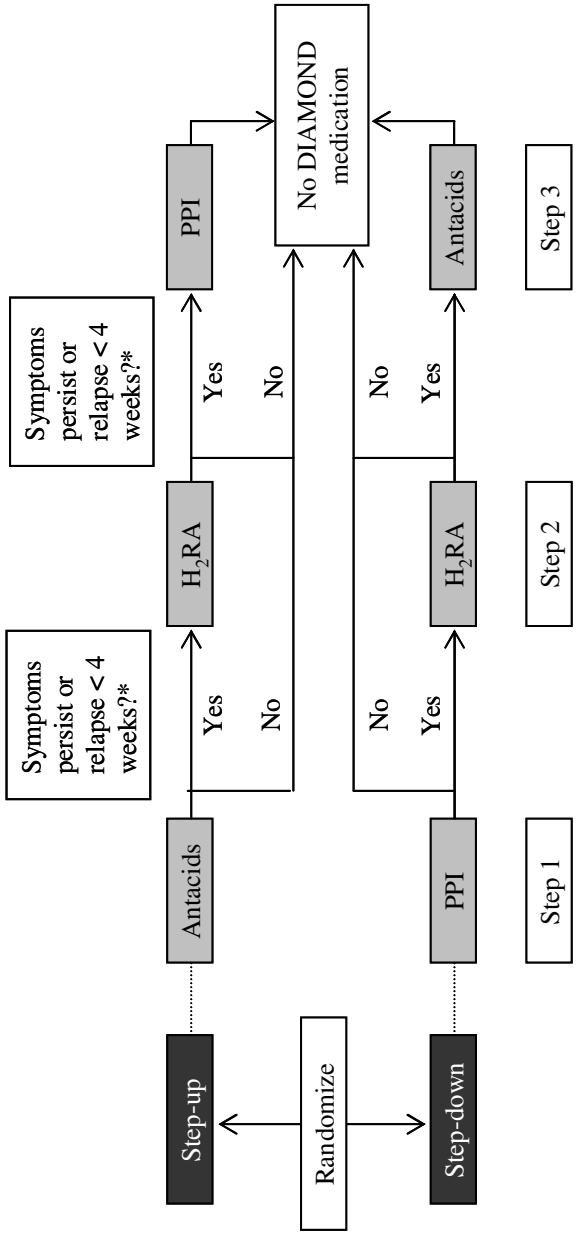


Figure 7.1. DIAMOND: treatment strategies.

* If the symptoms persisted the patient continued with the next treatment step. If the symptoms initially were relieved but relapsed within 4 weeks after stopping the treatment step, the patient also started the next treatment step. Otherwise (in the case of a relapse after 4 weeks), the GP could treat the patient to his/her own judgement.

The protocol of DIAMOND is registered on https://clinicaltrials.gov (clinicaltrials.gov identifier: NCT 00247715). It is a pragmatic, large, multicentre, randomised controlled trial in primary care, running from 2003 untill 2007, in which 664 patients with dyspepsia were included and more than 300 GPs participated. The study is conducted with the joint expertise of three academic research centres from both primary and secondary care. While within DIAMOND besides effectiveness also cost-effectiveness will be analysed, this paper will focus on the evaluation of clinical end-points. Economic evaluation trials are facing specific methodological challenges, which are described for instance by Ramsey et al.[3] and Tunis et al.[4]

Box 7.1. Aims of the DIAMOND-study.
Primary aim of DIAMOND: • To investigate which treatment strategy, 'step-up' or 'step-down' treatment, is the most (cost-) effective initial management strategy for patients with a new episode of dyspepsia in primary care.
Secondary aims of DIAMOND: • To investigate which factors influence the severity of the GI complaints. • To investigate which factors determine compliance with dyspepsia medication prescriptions and compliance with advised lifestyle changes. • To investigate which factors influence treatment success.

Challenges in designing a study

Choosing the right intervention and blinding treatment allocation

Pragmatic trials evaluate the beneficial effect of a treatment strategy for clinical practice when applied by any clinician to any patient with the disorder studied. The intervention must be relevant and feasible to be generalised to clinical practice and it must be compared to the best available usual care (reference care). Randomisation and blinding caregivers, participants, and investigators for treatment allocation are used in trial settings to increase the internal validity and aims to ensure that an effect is solely caused by the intervention.[5] Inadequate blinding in trials proved to result in 30% lower odds ratios than adequate blinding.[6] However, in every day practice treatment is not blinded, and may be influenced by prejudices of GPs or patients. While blinding is important to increase internal validity, it may limit the generalisability of results. Furthermore, blinding treatment allocation is often difficult to achieve in pragmatic trials, because of differences in the appearances of various treatments (for instance operation versus medication) or differences in the consultation scheme.

One possible solution is cluster randomisation,[5] where one group of caregivers exclusively prescribes the experimental treatment and another group exclusively the

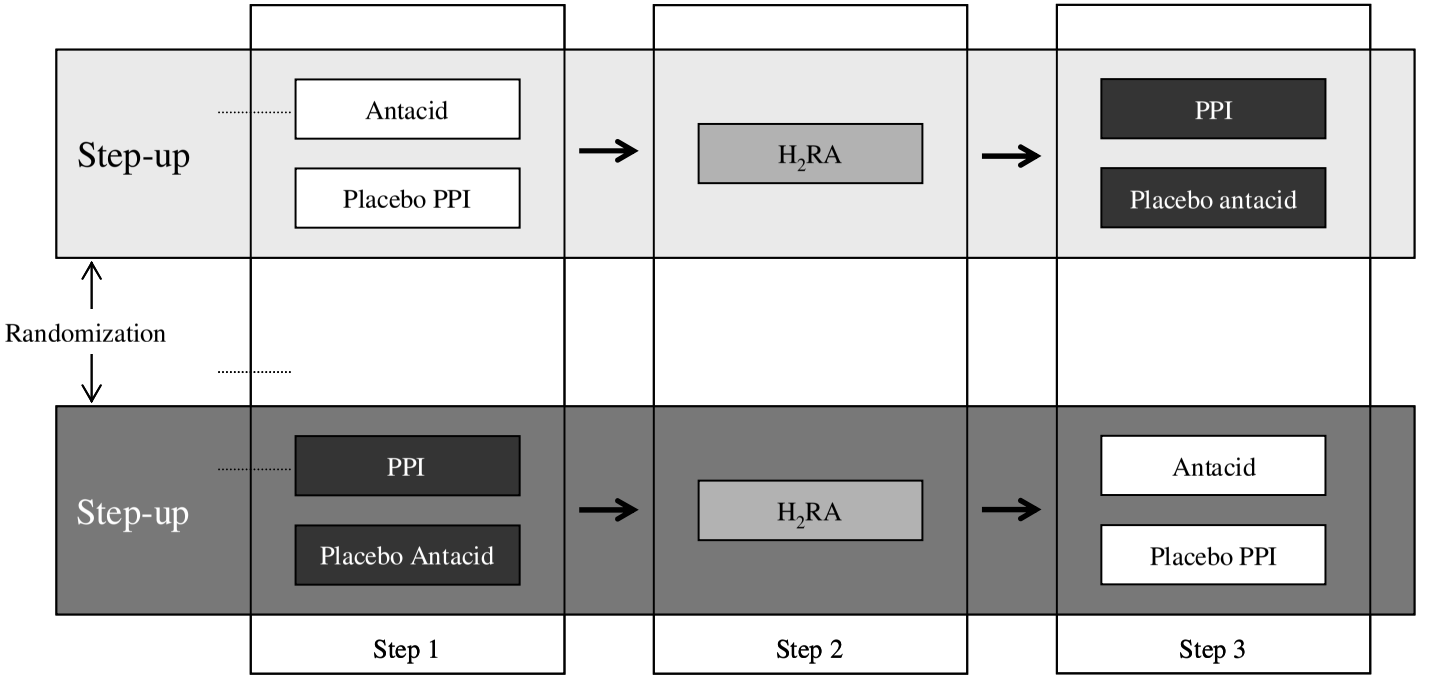
reference treatment. When all physicians within one centre are allocated to the same treatment arm, contamination will be reduced and all patients within one centre get the same treatment. Nevertheless, prejudices of caregivers, patients or researchers might still cause biases, for instance if the treatment is terminated preliminarily when physicians or patients do not expect the treatment to work. Although this reflects every day practice and might not be a problem in pragmatic trials (as long as patients are still included in analyses), observation bias decreases internal validity. Furthermore, because differences between caregivers can bias the results, one should then adjust for these differences with multi-level analysis.

The rationale behind our choices

The DIAMOND project was designed to compare a 'step-up' treatment strategy (Figure 7.1) (which is advocated in recent Dutch guidelines) with PPI-treatment (which is practised by many GPs). The appearances of both strategies differ too much to be suitable for blinding. Therefore, we decided to compare the 'step-up' treatment strategy with a 'step-down' treatment strategy, in which the PPI-treatment is followed by two treatment steps (Figure 7.1). Both treatment strategies were now made comparable in drug distribution and appearances by using placebos (Figure 7.2). This had several advantages; first, this design enables to investigate whether patients experience symptom relief on other (non-PPI) acid-suppressants when initial PPI-treatment fails. Second, PPIs can have a known rebound effect. In the 'step-down' group it is possible to investigate whether patients, who initially responded well on PPIs but got a relapse, respond equally well on other (cheaper) acid-suppressants. Third, when patients needed all three medication steps, both groups received the same medication, only in a different order, so the influence of the order of medication on for example patient satisfaction can be investigated.

Our design also had some disadvantages. Our organisation of 'step-down' treatment does not reflect usual care, which might affect generalisability. Some argued it is unethical to 'step-down' when the strongest drug is not effective. However, in our opinion patients can safely try the other two kinds of medication, before further investigation is established. Furthermore, in both groups patients had to use a placebo along with normal treatment. This can be a burden, since it means taking extra pills in step one and step three, and it differs from everyday practice too.

Figure 7.2. DIAMOND: blinding of the treatment strategies.



*Antacid: algedrate-magesiumoxide; H_2RA: raniditine; proton pump inhibitor (PPI): pantoprazole.

Although heavily aimed for, we were not able to find completely identical placebos. However, patients would not be able to tell their treatment allocation and to ensure that GPs would not recognize the pills, non-transparent medication jars packed in sealed paper bags were used. Clustered randomisation as discussed above could have induced more bias as the treatment allocation would have been recognized easily by GPs after completing the first patient in their cluster.
We chose to disclose treatment allocation at six months, just after measuring primary outcome. We reached high internal validity at the cost of decreasing external validity. Primary outcome (adequate symptom relief according to the patient) was measured at six months, which could be three to four months after prolonged prescription of any medication chosen by the GPs after completing the trial. In usual care the GP would repeat prescription of the most effective on recurrence of the symptoms. However, because of the 'late' disclosure of treatment allocation in DIAMOND, our GPs may have assumed that symptom relief may have occurred during the use of PPIs and prescribed this after the trial medication was finished, while maybe the patient responded on the antacid. Consequently, blinding might have caused convergence of treatment after trial medication in both strategies, which decreases differences in measured effectiveness.

Infection with Helicobacter pylori can influence the effectiveness of treatment as well as relapse rates of symptoms. Therefore blood samples for serology were taken at baseline. The H. pylori test results were also disclosed at six months to avoid the treatment or costs to be influenced by H. pylori management before measuring primary outcome. Incidentally GPs requested to disclose H. pylori test results earlier, in which case, the (theoretical) costs of H. pylori testing were included for the cost evaluation of treatment. The medical ethics committee agreed with postponed disclosure since H. pylori infection takes place early childhood and has no imminent association with the onset of symptoms. Early H. pylori testing in this trial may have caused GPs to be more aware of H. pylori infection and may have urged them to inform about the test results more often than in normal practice. However, the alternatives, drawing blood samples only when a test is requested by the GP or after follow-up is completed, would have caused more drop-outs. The choice to communicate H. pylori test results at six months and take theoretical costs into account when requested sooner is a clear example of a way to control the treatment, while it probably decreases the external validity.

Our choices may all influence treatment effects. We believe that blinding the treatment allocation and the use of placebo led to more comparable treatment strategies, which probably led to a smaller difference between the true effects of both treatment strategies than in every day practice would exist.

Choosing an appropriate study population

Regarding internal validity, according to Kleinbaum et al.[7] selection bias is a distortion in the estimate of effect resulting from the manner in which subjects are selected from the target population. Within DIAMOND all patients were randomly allocated to either the 'step-up' or 'step-down' treatment strategy, which makes selection bias unlikely.

Regarding external validity, it is very important that the investigated population should represent the target population, but how can optimal representation be achieved? First, the target population needs to be clearly defined by using inclusion and exclusion criteria. Second, the method of patient selection greatly influences representation (see 'Patient recruitment'). The best way is to select patients randomly, but this is very challenging because it is difficult to avoid self-selection. Responding to an advertisement is a clear example of self-selection. Also GPs may be self-selected if they responded to an invitation letter to participate. This can be a problem when the participation of the GPs is associated with certain patient characteristics (education level, co-morbidity).

A representative patient sample must reflect all patients in the target population, including patients from minority groups, especially when treatment effects are supposed to be influenced by population characteristics. Translated questionnaires should enable immigrants to participate. Consideration should always be given to motivate patients expected to have low participation rates, for instance by tailoring patient information to gender or age.

There are several practical or judgemental reasons (lack of time, symptoms, preference, willingness) for a patient not to be included although eligible. Therefore, registration of all eligible patients and monitoring reasons for non-inclusion is preferred, to be able to judge inclusion selection. However, this is time consuming and researchers still would question the completeness of the registration. When available, electronic medical records might be helpful in estimating the proportion of non-included eligible patients. However, routine electronic medical records might also lack data to check eligibility (e.g. duration of symptoms) and will not always provide insights in the reasons for non-inclusion.

The rationale behind our choices

We chose to focus on 'adult patients with a new episode of dyspepsia', because the most effective treatment for these patients was unknown. Careful consideration with all the experts in the research board led to a limited number of inclusion and exclusion criteria to define these patients. The criteria were based on recent guidelines and were judged to be feasible and clear (Box 7.2). Regarding the representation of minority groups, it was not possible to make all relevant language adjustments, but translation from Dutch into English was provided. Some participating immigrants who spoke other languages had help from their relatives to fill out the questionnaires.

Box 7.2. In- and exclusion criteria of DIAMOND.

Inclusion criteria:
- Visiting the GP for complaints of which the GP thinks that they originate from the upper GI tract and for which acid-suppressive medication can be effective;
- 18 years or older.

Exclusion criteria:
- Usage of prescribed acid-suppressive medication in the last 3 months before inclusion;
- Gastroscopy during the year prior to inclusion;
- Presence of alarming symptoms;
- Presence of contraindications for prescribing acid-suppressive medication, such as pregnancy, liver or kidney malfunction;
- Inability to fill out (Dutch) questionnaires, for example because of language problems.

Patients were recruited by participating GPs. We invited as many GPs as possible within our geographic boundaries, resulting in 312 participating GPs distributed over the Netherlands (Figure 7.3). It is possible that especially GPs with a special interest in the gastrointestinal (GI) field were responding. This can be a problem if participation of the GPs is associated with effect modifying patient characteristics. However, it is likely that the heterogeneous group of participating GPs (GPs from urban as well as rural regions with solo, duo, or group practices) has resulted in a heterogeneous patient sample, which represents the primary care population.

To investigate initial treatment of patients with a 'new' episode of dyspeptic symptoms, patients who used prescribed acid-suppressive drugs in the last 3 months were excluded. However, since patients with mild symptoms are more likely to be without medication for more than three months than patients with severe symptoms, this might have resulted in a patient sample with overrepresentation of patients with mildly severe dyspepsia. Moreover, maybe the GPs only invited patients with mildly severe dyspepsia, because they did not want to risk patients with more severe complaints to be treated with the 'step-up' treatment strategy. Finally the representativeness of our sample will be investigated by comparing several relevant patient characteristics to results from other (preferably population based) studies.

Hypothetically, the difference in treatment effect between PPIs and antacids might be smaller in patients with mild symptoms. As a consequence the difference between

the two treatment strategies might have been smaller than in every day practice where also patients with more severe complaints are treated.

Choosing the essential outcome measurements

The value of study results is greatly determined by the definition of the primary outcome and choice of measurements. When the primary outcome is an objective measure, e.g. survival, it is easy to measure and define it. However, the outcome of many diseases in primary care needs more subjective evaluation, and selection and definition of the outcome may prove to be difficult. A proper definition can be based on literature or expert opinion. Furthermore, it needs to reflect what decision makers want to know. The endpoint also needs to be clear, and preferably comparable with other studies.

Concerning the measurements, the validity and reliability should always be critically assessed. To increase response rates questionnaires must be as short as possible. This is challenging, especially when several additional research questions are investigated as in our study (see Box 7.4). The additional value of every question in the questionnaire needs to be critically judged and a pilot study is preferred to estimate the feasibility and burden for GPs and patients.

The rationale behind our choices

Choosing the primary outcome measure for DIAMOND was not easy because[8] the presence or absence of 'dyspepsia' can not be measured objectively. Furthermore, dyspepsia is characterized by periods of remission followed by symptom relapse. We used 'adequate symptom relief at six months, according to the patient' as primary outcome, following expert recommendations (Rome II criteria) and because this reflects the decision to stop or continue treatment in every day practice. It is generally accepted that symptomatic response can be used in dyspepsia because this is what GPs have to rely on in clinical practice. Besides, more objective measurements (e.g. endoscopy) poorly correlate with symptom severity. To enable a comparison with results from other studies we analysed the change in severity of the gastrointestinal symptoms and quality of life as secondary outcomes.

Additionally, choosing the right timing of the measurement of the primary outcome in a study with multi-step treatment strategies is difficult. Choosing a six month time interval is convenient for policy makers and feasible in trial practice. But the downside is that patients received trial medication for variable periods of time. Good responders may only have had the first treatment step, and if they remained

symptom-free for four weeks after finishing treatment they did not start with the second treatment step. In the case of relapse after four weeks or after finishing treatment step three treatment was left up to the GP. As mentioned above, the primary outcome might be influenced more by the GP prescribed medication than by the study medication at the time of six months. This may have decreased differences between the treatment strategies at six months. We also measured short term outcomes (at two weeks, four weeks, etc.) to be able to determine the short-term efficacy of the individual treatment strategies.

We investigated the validity of the questionnaire for the severity of gastrointestinal complaints.[9,10] A pilot study among non-experts to investigate the burden of filling in our questionnaires showed that at baseline as well as at follow-up 15 to 30 minutes were needed for a complete response. This was judged to be acceptable and patients were informed of this time estimation before providing informed consent to participate.

Box 7.3. Measurements.

Primary health outcome:
- Adequate symptom relief at 6 months according to patients.

Secondary health outcomes:
- Severity of the GI complaints (at 2 weeks and after the treatment step);
- Quality of life at 6 months (at 2 weeks and after the treatment step).

Additional research questions investigated:
- The cost-effectiveness of both treatment strategies;
- The association between genetic determinants and dyspepsia and treatment success;
- Compliance with prescribed medication advices and life-style advices and which factors influence compliance;
- The association between psychosocial determinants and dyspepsia and treatment success.

Self-administered questionnaires used:
- General questionnaire to measure effect of the treatment, costs, work absenteeism, demographical determinants, co-medication used and life-style;
- Gastrointestinal Symptoms Questionnaire;
- EuroQol 5D;
- SF 36;
- Compliance Questionnaire;
- SCL 90;
- Health Hardiness;
- Utrechts Coping List;
- Major Life Events.

Challenges in conducting a study

Patient recruitment

Many studies fail to recruit enough patients which compromise statistical power. A review by Mc Donald showed that only 31% of randomised controlled trials were able to reach their goals concerning patient recruitment.[11] There are several ways to recruit patients: from medical records, by advertisement or during consultation. The usage of medical records increases effective recruitment because it does not depend on patient presentation to recruiters during the inclusion period. However, this method can not be used when incident cases are required. Sellors et al.[12] found

barriers such as the availability of electronic medical records, the experience of office staff and GPs to produce patient sampling frames and ethical considerations. Another method is patient recruitment via advertisements in (local) media or via flyers at the GP's office. However, patients responding to such advertisements may differ from patients not responding which leads to selection bias and hampers external validity. The conventional way to recruit patients is by the GP during consultation (incident cases). This way of recruitment approximates routine practice the most, which increases external validity. However, it poses a huge burden on the GP and is not always successful. There might simply be a lack of eligible patients or trial procedures can be too restrictive. According to Van Der Windt et al.[13] the main reasons for not referring eligible patients to the research centre by participating GPs were: busy surgery hours, forgetfulness, or the conviction that a patient would benefit more from a specific intervention. De Wit et al.[14] found that successful patient recruitment in a dyspepsia trial was determined more by the motivation of GPs by the research group than by financial incentives, research topic, or research experience. Foy et al.[15] investigated in a meta-analysis the impact of interventions on patient recruitment and concluded that organisational characteristics (e. g. strong trial infrastructure) seemed to be important. Furthermore, many interventions on patient recruitment were not evidence-based but based on the experience of the investigator.[15]

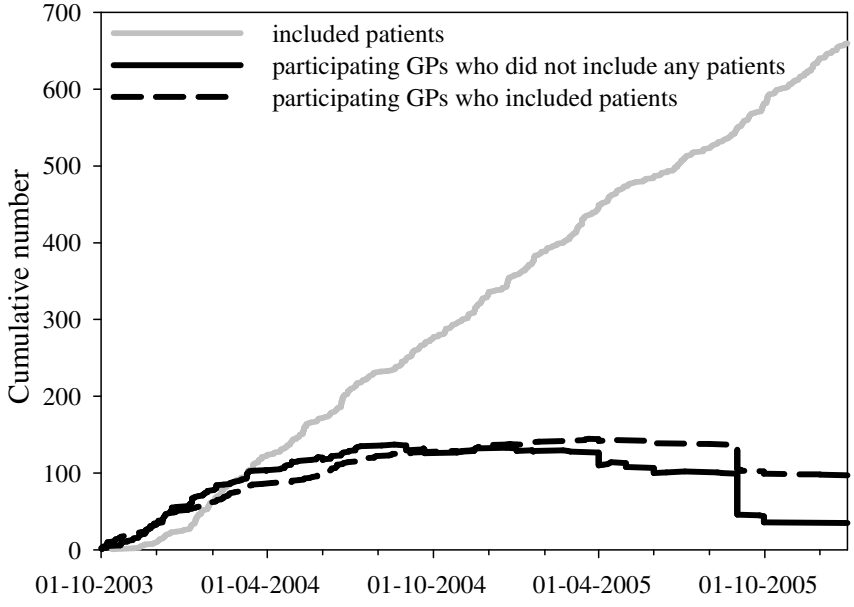
Additionally, successful patient recruitment depends on the patients' motivation. Chang et al.[16] found that the reasons for patients to participate could be divided into six general categories: 1) benefit to self; 2) benefit to others; 3) gratitude to the physician; 4) positive comments by the trusted professional; 5) the appearance, personality, manner and gender of the recruiter; 6) monetary compensation. We agree with Chang et al.[16] that the most effective recruitment involves a direct and personal approach. Patients appeared to enjoy being noticed and sorted out for something presented to them as important and special. The patient information and the GP need to address possible reasons and advantages for patients to participate.

The rationale behind our choices

Since we focused on patients with a new episode of complaints, we chose to recruit incident cases during consultations by the GP. To our experience successful patient recruitment depends on: 1) Close monitoring of recruitment statistics and extra measures to boost recruitment if necessary; 2) flexibility of the research protocol: it must be possible to adapt the protocol when GPs cannot use it in practice or when

selection criteria are not clear or too strict; 3) good and regular contact with the GP or an assistant (preferably face-to-face or by telephone), which enables to remind and motivate them and notice and resolve difficulties. We visited the GPs after each new included patient to collect the patient's blood sample and provide new materials. The purpose of this visit was to reinforce the patient inclusion, but not to discuss how the included patient was treated to avoid an extra educational intervention. Furthermore, a monthly newsletter was sent to the GPs to remind them and to keep them posted. We tried to minimize the burden for the GPs and the assistants (for instance by taking blood samples ourselves when necessary) and answered questions promptly implying easy accessibility. Despite these efforts to motivate and assist the GPs, only 48% of the participating GPs recruited one or more patients (Figure 7.4).

Figure 7.4. Patient recruitment and number of (successful) GP participants.



We can only speculate on the reasons for this disappointing number: maybe the inclusion and treatment was expected to be too time-consuming or maybe these GPs simply forgot to invite eligible patients despite of several reminders. Social desirability may have caused GPs to participate who were less motivated to include patients. Although ultimately successful, patient recruitment was very time consuming and needed sufficient budget for recruitment personnel. The intended

inclusion period of two years had to be prolonged in October 2005 to include the desired number of patients. Only GPs who were expected to include several patients before the end of 2005 ('promising' GPs) were invited to continue patient recruitment.. This explains the sudden fall in participating GPs in Figure 4. Interestingly, this did not decrease the patient inclusion in the last months, which suggests that it may be more efficient to only include highly motivated and 'promising' GPs. Exclusion of reluctant GPs may hardly decrease inclusion rates but does decrease the workload for the researchers.

GP recruitment

Patient recruitment in primary care based trials often depends on the cooperation of GPs. Since the demand on GPs to participate in research is growing and it is hard to keep the balance between research participation and daily practice,[14] GPs must be very critical in their decision to participate. Factors known to influence the physician's decision to participate include:[17-19] 1) a personal interest in the research topic; 2) the relevance of the research question; 3) the personal connection with the researchers; 4) the collective ownership of the project; 5) the support of stakeholders or respected members of the professional community; 6) the revenue of costs associated with research participation; 7) the simplicity of protocols with low interference with patient care; 8) the availability of practice staff to assist the enrolment; 9) the timeliness of patient recruitment; 10) the satisfaction with study participation. Van Der Windt et al.[13] also mentioned that (accredited) postgraduate training is a reason for GPs to participate, and involvement in too many other studies is a reason not to participate.

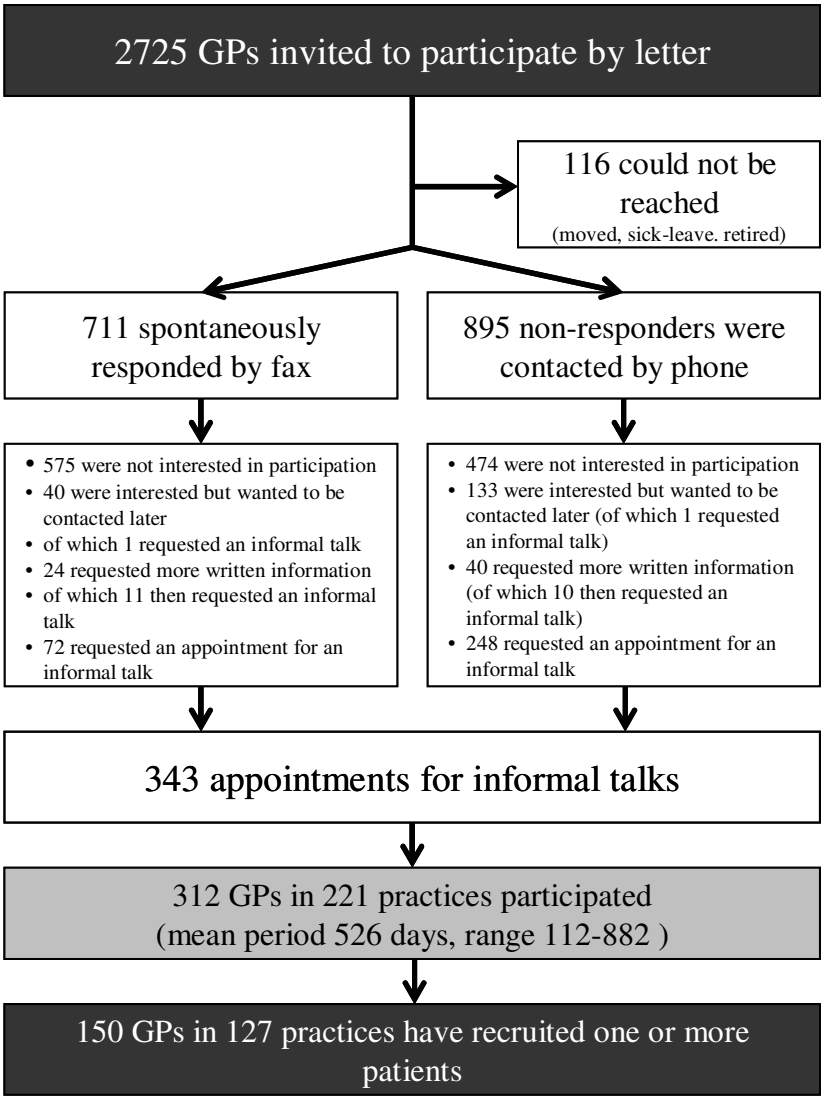
A strategy for approaching primary care settings as proposed by Murphy et al.[17] and Kocken et al.[20] recommends identification of stakeholders and regional opinion leaders, using support letters by relevant professional organisations and supplying adequate, but concise, information. It is important to consider and address the reasons for GPs to participate during the recruitment.

The rationale behind our choices

For GP recruitment we wanted to invite as many GPs as possible within our geographical boundaries to gather a large heterogeneous GP sample. We retrieved the addresses of all eligible primary care settings from a registration at the three participating universities. The GPs received an invitation letter with information

about the research together with a recommendation letter from the Dutch College of General Practitioners and the Dutch Institute for Healthcare Improvement.

Figure 7.3. GP recruitment.



A reply form was offered to respond by fax. In the case of non-response the GP was invited again by means of a telephone call. After an informal appointment at the GP's office, the GP decided whether or not to participate. For practical reasons the

GP recruitment was spread out over the first period of patient inclusion. The results of GP recruitment are given in Figure 7.4. To our experience, however ultimately successful, the GP recruitment was very time consuming because of the many phone calls and visits. Although difficult, personal contact with the GP more positively influenced participation than leaving a message with the assistant. Spreading out the GP recruitment period gave us the opportunity to adjust the information letters and to approach more GPs to boost patient recruitment when the inclusion lagged behind. Our method of GP recruitment probably has resulted in a heterogeneous and representative relatively large GP sample, which is likely to have a positive influence on the generalisability of the results.

Protocol deviations

Protocol deviation or protocol non-adherence by patients, GPs or researchers is common. Examples of protocol deviations are: drop-out, inclusion of ineligible patients, not receiving the allocated treatment, unplanned interruption or abortion of treatment; and not taking the trial medication as prescribed. Drop-outs are patients who stop their trial medication but remain available for follow-up.[21] Patients can also be 'lost to follow-up', when they are no longer accessible to the investigators.[21] Eligibility errors are relatively common.[21] Objective eligibility criteria are less prone to error than subjective ones. If eligibility is checked before randomisation, the consequences of such errors will be minimal. However, in pragmatic trials commonly the eligibility is checked e.g. with blood measurements or patient self-reports, which are often only available after randomisation.

Bias can be introduced when protocol deviation affects both treatment groups differently.[21] Researchers therefore investigate whether the protocol deviation is caused by systematic or random errors, and whether it causes differences between both treatment groups. When protocol deviation is associated with one treatment arm (e.g. if the experimental treatment has more side-effects), it is important to take this into account because protocol deviations will also happen in every day practice. In a per-protocol analysis all patients with a protocol deviation will be excluded,[22] which contrasts with the purpose of conducting a pragmatic trial. Exclusion of patients can result in bias when the patients that stay included are no longer representative for the study population. Therefore, a per-protocol analysis is less suitable than an intention-to-treat analysis for pragmatic trials. Some pragmatic trials perform a per-protocol analysis additionally to an intention-to-treat analysis, but difficulties arise when both analysis produce different results. Whereas the results of

a per-protocol analysis may provide additional insights in why a treatment has (or lacks) effect in every day practice, in pragmatic trials the intention-to-treat analysis is the way to determine the overall effect.
Protocol deviations can partly be prevented by writing simple and clear protocols, providing proper patient information, and by closely monitoring GPs and patients during a pilot study and adjusting the protocol if required.

The rationale behind our choices
To reflect every day practice as much as possible we chose to write a flexible treatment protocol, in which for instance the GP was free to decide when patients could return for consultation (after four weeks was recommended) or how the consultation was done, by phone or personal. This has probably minimized our number of protocol deviations. We can only present some preliminary data at this moment, since not all analyses have yet been finished. No non-eligible patients were included. Eleven patients gave an informed consent but changed their mind shortly after and they did not start using our trial medication. One patient did not use medication step 1 for unknown reasons, but started medication step 2 approximately two weeks after baseline. Table 7.1 shows the questionnaire response rates and suggests that number of patients 'lost to follow up' was limited. For the intention-to-treat analysis, preliminary results indicate that for 98% of the patients the primary outcome at six months is present. We are able to achieve such a high response rate by contacting all non-responders or drop-outs by phone or via the GP (except for patients indicating not to be willing/able to participate anymore) and asking them to answer the question: has symptom relief been adequate since the start of the treatment? Most patients are willing to answer this single question.
Some patients do not return the initial six month questionnaire, because they think that when their complaints are resolved they do not need to return questionnaires. To prevent this bias we send reminders pointing out the importance of always returning the questionnaire and contact non-responders by phone or via their GPs. The preliminary response rates for all questionnaires are given in Table 7.1. The response rates slowly decrease in time as can be expected. The length of the baseline questionnaire and the high number of questionnaires during the first month caused several patients to stop their participation. Although tested in a pilot study and explained in the patient information, this could not be completely prevented. Maybe in the near future easier ways to monitor complaints and retrieve important

data (e.g. via the internet) will become accessible and can facilitate patient cooperation and prevent drop-out.

Table 7.1. Preliminary results*: the patient questionnaire response rates.

N=664*	At baseline	At 2 weeks	After step 1	After step 2#	After step 3#	At 6 months	1 year
Sent out	664*	613*	643*	595*	587*	659*	566*
Returned	629	543	525	474	454	646	373
Response rate	95%	86%	82%	80%	77%	98%	66%^

*Not all follow-up questionnaires were sent out, for instance when patients started step 2 within 2 weeks, or patients reported they no longer whish to receive questionnaires.
#if medication of this step was not started, questionnaires were sent out at 2 resp. 3 months.
^In the case of non-response a reminder is sent out after all questionnaires except after 1-year, since this is an additional measurement to the original research protocol. This explains the low response rate.

The consequences of our choices for the usefulness and relevance of the DIAMOND results

The results of this study are useful/relevant for policy makers, patients, GPs and researchers because a large population of well defined patients, which is generalisable to the Dutch population of patients with a new episode of dyspeptic symptoms. The study has a high internal validity because of the random treatment allocation, and the concealment of treatment allocation/blinding, which increases the value of the results for policy makers. However, the external validity is decreased by the use of 'step-down' treatment instead of PPI-treatment (which is more common in every day practice) and by the blinding. Consequently, it is difficult to say what the effect of both treatment strategies will be if performed in every day practice.
In order to adapt the study protocol to routine daily practice, a multistep protocol was designed. Although this resembles everyday practice it makes analysis more difficult, because not all patients are in the same treatment step at a certain point in time, and because the period of time between finishing the trial medication and registration of the primary outcome may vary from patient to patient. In case this period is long, the primary outcome may be influenced by follow-up treatment chosen by the GP. This may decrease any differences between the treatment strategies, but on the other hand the primary outcome does provide essential

information about the effectiveness of actual primary care treatment for dyspepsia. Furthermore, the differences between the two treatment strategies can be analyzed in more detail by analyzing the secondary endpoints (at 4 weeks, 12 weeks, etc…). Therefore, the trial design as presented will provide important insights in various strategies for treatment of dyspepsia in primary care.

Box 7.4. DIAMOND inclusion and treatment protocol.

1. When a patient visits the GP, the in- and exclusion criteria are checked.
2. When the patient meets the criteria, the GP informs the patient about DIAMOND. When the patient wants to participate, he or she provides an informed consent.
3. The GP hands out the patient the medication for step 1. The medication is packed in boxes and is provided to the GP at the start of the study. Each box contains all the medication steps for one patient. The patient numbers on the boxes are linked to the numbers on the randomisation list in a sealed envelope.
4. A blood sample is taken.
5. The patient receives the first questionnaire from the GP to fill out at home. Other questionnaires are sent to patients. (see Box 7.3).
6. The patient is treated according to the treatment protocol (see Figure 7.1a and 7.1b). If the symptoms continue or relapse within 8 weeks after starting the medication step, the patient starts with the next treatment step. It is possible to shorten the treatment steps into less than 4 weeks, for instance when the patient suffers from side effects. The patient and GP are advised to schedule a follow-up visit at 4 weeks, which should be cancelled when the complaints are resolved.
7. When symptoms continue or relapse after medication step 3, the GP can treat the patient according to their own judgement.
8. The GP and the patient are informed six months after inclusion about the treatment allocation and the test results from the blood sample (whether the patient was infected with *Helicobacter pylori*).

Summary

Pragmatic trials must ensure a high generalisability without compromising internal validity, which is very challenging.[23] Therefore, a critical appraisal of the planned design and method to conduct the trial before actually starting to collect data is essential. When several publications on patient recruitment or other pitfalls in designing/conducting a pragmatic trial are consulted, one may increase the likelihood of conducting a successful trial. Furthermore, it is very important to set priorities beforehand where on the 'spectrum from explanatory to pragmatic' you want your trial to be: do you want to know the 'unbiased' effect of the treatment (as in explanatory trials) or are you more interested in the effects in daily primary care (as in pragmatic trials)? For instance, we chose to blind treatment allocation because otherwise prejudices of GPs, patients and researchers might have biased the results, although blinding contrasts with the purpose to reflect every day practice in pragmatic trials. On the other hand, we chose to use flexible treatment protocol to reflect every practice, what again might contrast with using standardized treatment in explanatory trials.

This paper shows that while we did not compare the two most frequently used treatment strategies in the DIAMOND-study, we were still able to collect highly valid data because of the blinded randomised treatment, the randomly selected heterogeneous patient sample and the research protocol that closely fits to normal practice. Although it is very difficult to recruit as many GPs and patients as needed, success can be determined by careful consideration of how the GPs and patients will be optimally recruited and what their reasons to participate or to refuse participation will be. Our experiences with the DIAMOND-study give an indication of what success rates regarding GP and patient recruitment and questionnaire response can be expected in similar studies.

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