Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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Aims and Background of this thesis
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Dyspepsia in General Practice

Dyspepsia with its great variety of symptoms is common in the general population and is experienced at least once a year by 30-40% of the population in Western countries. Only about one quarter of the symptomatic persons consult a physician. Patients present their complaints to the general practitioner (GP) often as upper abdominal pain or discomfort, bloating, nausea, vomiting, early satiety, upper abdominal fullness, heartburn or acid regurgitation. After taking a careful history and physical examination patients in primary care are usually treated empirically. Only patients with alarm symptoms (e.g. weight loss, melaena) are immediately referred for additional diagnostic procedures like upper endoscopy. In the Netherlands, the Guideline on the management of stomach complaints, published by the Dutch College of General Practitioners (in 1994 and revised in 1996 mainly due to changes in management of *H. pylori* infection), has proposed an initial management of dyspepsia that is based on the most important symptoms, categorised in subgroups; ulcer-like, reflux-like, and non-specific dyspepsia. Furthermore life-style aspects, medication such as NSAIDs, and emotional disturbance are considered as possible causal factors for dyspepsia and need exploration. Short-term medication is prescribed in 70-90% of first consultations. Treatments include antacids, prokinetic drugs, antibiotics, *H₂*-receptor antagonists, proton pump inhibitors and mucosa protective agents.

In the Netherlands, for patients with persisting dyspeptic symptoms after initial empirical treatment, the GP is able to refer for upper intestinal endoscopy facilities without involvement of a hospital specialist. This open-access endoscopy system is available since early nineties. In the Netherlands, 15-20 % of the primary care patients with dyspepsia is eventually subjected to further diagnostic procedures including gastro endoscopy. After upper endoscopy, patients with dyspepsia can be subdivided into three main categories: (1) those with an identified cause for the symptoms (e.g., chronic peptic ulcer disease, gastro esophageal reflux disease with or without esophagitis (GERD), malignancy, pancreatic-biliary disease, or as side effects of medication), (2) those with an identifiable pathophysiological or microbiologic abnormality of uncertain clinical relevance (e.g., *Helicobacter pylori* gastritis, histological duodenitis, gallstones, visceral hypersensitivity, gastro duodenal dysmotility); and (3) those with no identifiable explanation for the symptoms. Patients with no definite structural or biochemical explanation for their symptoms (i.e. category 2 and 3) are considered to have functional dyspepsia.

At upper endoscopy, a minority of patients has organic disease of clinical significance such as peptic ulcer disease (PUD) (5-15%) or GERD (25-30%). Malignancies are very seldom found (< 2%). Most of the primary care patients (60-70%) do not have any recognisable organic disease and are labelled ‘functional dyspepsia’.
Definition, presentation and prognosis of dyspepsia in general practice is in various aspects different from dyspepsia in secondary care. Firstly, the definition of dyspepsia differs. Recently, the predominantly specialist Rome working party on Functional Gastrointestinal Disorders has updated the definitions for dyspepsia and other functional disorders. Epigastric pain or upper abdominal discomfort are the cardinal signs of dyspepsia and symptoms of heartburn, which is felt to be indicative for GERD, are not more classified as dyspepsia. At the moment this definition does not fit with the conceptual framework in general practice in which also heartburn and acid regurgitation are part of the symptom complex of dyspepsia. Secondly, patient populations differ between primary and secondary care. As aforementioned, only 15-20% of dyspeptic patients from primary care are referred to gastroenterologists or sent for additional procedures (e.g. upper endoscopy). As a result of this selection of patients (‘referral filter’) a specialist sees relatively more cases with organic disease. This may give a specialist another view on management of dyspepsia in comparison to the general practitioner, who mainly bases his treatment strategy on probabilities and empirical treatment response, which may change in time. Therefore, results from specialist studies cannot always be easily generalised to the general practice situation.

Last decades, initially based on symptoms, however after upper endoscopy often based on the diagnosis of PUD, esophagitis gr 1-4, relapsing symptoms of reflux disease or functional dyspepsia, patients both in primary as in secondary care were advised to take life long acid suppressant drugs (ASD) daily. The Dutch Guidelines advise a yearly evaluation of symptoms and, if feasible, cessation of medication. No data are available how these guidelines are followed. Many of these patients are “invisible” for the GP since they are treated with routinely repeated prescriptions for ASD without further consultation. These acid suppressant drugs, especially the H$_2$-receptor antagonists (H$_2$ RA) and the proton pump inhibitors (PPI) have been already for years the world’s most frequently prescribed medications. This prescription pattern has large economic consequences. In the Netherlands, the expenditure on ASD accounts for 10% (around 300 million Euro) of the annual national pharmacotherapy budget already for several years.

Chronic use of ASD by patients in general practice in other countries than in the Netherlands varies from 2%-5%. It is questionable whether such drugs are still being prescribed and used in an efficacious way, since the view on management of dyspepsia has changed in several aspects. The subject of this thesis is to find out whether ‘tapering the long-term use of ASD in chronic dyspeptic patients in general practice’ is feasible and adequate. This thesis focuses on chronic dyspeptic patients long-term on ASD in general practice having peptic ulcer disease, gastro esophageal reflux disease (symptomatic or erosive grade 1 (Savary-Miller)), functional dyspepsia or “uninvestigated” dyspepsia.
Overall aim of this thesis:

To investigate the feasibility of reduction of the long-term use of acid suppressant drugs in chronic dyspeptic patients in general practice and interventions by which this could be achieved.

Since no data were available on chronic use of acid suppressant drugs for the Netherlands, a pilot study was undertaken in 24 general practices.

Sub-aim 1

* To analyse long-term acid suppressant drug use in general practice (chapter 1)

Risk factors of dyspepsia and long-term use of ASD

- Psychology and health status

For long, dyspeptic symptoms were thought to be associated with psychological factors, like life-events, stress, anxiety, depression and personality disorders. Especially, in the 80's many studies were undertaken to explore those mechanisms. Conclusions were often conflicting. However, it might be that in a subset of dyspeptic patients, dyspeptic symptoms or an alteration of symptoms create anxiety for a serious disease or that stress or other psychological disorders create dyspeptic symptoms by altering the gut pain receptors. In primary care, health status of chronic dyspeptic patients is seldom investigated.

Sub-aim 2

* To compare the prevalence of psychological disorders and the health status of chronic dyspeptic patients in general practice with a control population (chapter 2)

- Helicobacter pylori

Although microorganisms might have been noticed in the mucus layer for more than a century ago, it lasted until 1983 when Helicobacter pylori (at that time called Campylobacter pyloridis and later changed to Campylobacter pylori) was identified by Warren and Marshall. For decades it was thought that the stomach was sterile owing to profound acid production and bacteria were only noticed after prolonged strong acid suppressant therapy. It is now well recognised that some gastric cancers, most duodenal and gastric ulcers are associated with H. pylori infection. The role of H. pylori in reflux disease (GERD) is not clear. No evidence is available for an etiologic role of H. pylori in GERD.

The role of H. pylori in functional dyspepsia is controversial. It is controversial whether
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maintenance ASD therapy increases the rate of development of atrophic gastritis in *H. pylori* positive patients, which is considered to be a pre-malignant condition.\(^{36}\)

Histological and bacteriological assessment of gastric biopsy specimens obtained by gastroscopy, has the highest accuracy in detecting *H. pylori*, but endoscopy is uncomfortable to the patient and expensive. The selection of *H. pylori* positive patients for endoscopic referral (‘test-and-endoscope’ approach), for *H. pylori* eradication treatment without endoscopy (‘test-and-treat’ approach) or for monitoring eradication of infection has become feasible by the development of non-invasive tests like serology\(^{27}\), urea-breath tests\(^{28}\) and the recently described assay to detect *H. pylori* antigens in stool specimens\(^{29}\). Usually, in dyspeptic patients ≥ 55 years endoscopy is performed anyway because the risk of cancer, so an *H. pylori* related PUD will be diagnosed. Since in patients younger than 55 years serious underlying organic disease is rare,\(^{7,30}\) the topic is whether patients without PUD could be excluded without performing endoscopy by these non-invasive tests. However, these tests are often validated in a patient population in a hospital setting and hardly evaluated in general practice.\(^{31,32}\) Furthermore regional validation of serological tests is propagated since the *H. pylori* antigens used in tests to detect the anti-*H. pylori* antibodies may be different from those present on the *H. pylori* isolated from other regions, thus influencing the discriminative ability.\(^{33,34}\)

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<th>sub-aim 3</th>
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<td>* to evaluate the ability of three non-invasive <em>H. pylori</em> tests (a whole-blood serology test, an ELISA test and a 13C-urea-breath-test) to exclude ulcer disease in chronic dyspeptic patients &lt; 55 years (chapter 3)</td>
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An other promising predictive test for PUD may be a serological test for detection of the more virulent CagA+ *H. pylori*, since CagA+ *H. pylori* has been found associated with peptic ulcer disease (PUD) in Western populations.\(^{35}\)

Policies to reduce the use of ASD

In this thesis we studied whether the use of maintenance ASD therapy could be reduced by eradicating *H. pylori*, by taking care of rebound acid hypersecretion after withdrawal of long-term ASD use, by using antacids as escape medication and by introducing ASD therapy on demand.

- *H. pylori* eradication
Successful eradication of *H. pylori* is difficult to achieve. Mono and dual therapies (a proton
pump inhibitor combined with a single antibiotic) are almost not or only moderately effective. Nowadays, the recommended eradication therapies, which are most efficacious, consist of a proton pump inhibitor, clarithromycin and amoxycillin or metronidazole, twice daily for at least seven days.\(^{20,24}\) The efficacy of regimens is jeopardised by poor patient compliance.\(^{35}\) In addition, infection with metronidazole- or clarithromycin-resistant \(H.\) pylori or with more virulent CagA-positive \(H.\) pylori strains may affect the efficacy of eradication therapies.\(^{36-39}\) A simple and highly effective \(H.\) pylori eradication regimen without serious side effects is essential to assure a high patient compliance. An optimal treatment still has to be established with respect to dose and also duration of treatment.

**sub-aim 4**
- to determine the efficacy of a four, seven and ten days triple therapy to eradicate \(H.\) pylori infection in patients with peptic ulcer disease (chapter 4)

**sub-aim 5**
- to determine the prevalence of CagA positive \(H.\) pylori infection, its relationship with disease and influence on the efficacy of \(H.\) pylori treatment (chapter 5)

- gradual reduction and stop
Rebound acid hypersecretion is a well-recognised phenomenon after withdrawal of long-term \(H_2\)-receptor antagonist therapy and has already been described in the eighties and early nineties.\(^{40-42}\) Although in the eighties animal models showed acid hypersecretion after cessation of therapy of PPIs \(^{43}\) studies since then have suggested that this phenomenon was not observed after omeprazole treatment in humans.\(^{44}\) However, more recent rebound acid hypersecretion is also found after long-term omeprazole treatment.\(^{45}\) The clinical significance of rebound hypersecretion remains unclear since the number of subjects included in these studies are small and mainly concern healthy volunteers. However, there is some evidence for a clinical impact of rebound hypersecretion. Rebound acid hypersecretion after \(H_2\)-receptor antagonist is accompanied by the onset of dyspeptic symptoms in previously asymptomatic subjects.\(^{46}\) In daily practice clinicians observe difficulties in patients in withdrawal of ASD because of severe resurgence of symptoms. We have tried to anticipate on the acid hypersecretion by asking the patients to taper the use of long-term ASD gradually within 3 weeks. It is investigated whether such an approach guided by the GP in this period of three weeks of gradual reducing the use of ASD, is beneficial.

- antacids as escape medication
Reflux symptoms were common (57%) in an unselected adult population (n=2500). However, only a minority of the symptomatic people (16%) take medication (most commonly antacids) and only 5.5% had sought medical consultation.\(^{47}\) In patients with
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oesophagitis, antacids are not more effective than placebo.\textsuperscript{44} Effect of medication, what ever, in functional dyspepsia is questionable.\textsuperscript{49} In mild reflux symptoms antacids may be helpful in relieving short-term symptoms.

- "on demand" ASD therapy.
The advent of H2-receptor antagonists was a major therapeutic breakthrough in the management of duodenal ulcer disease. Since relapse rates are high, 60-95\% ulcer relapse by one year, a significant group of duodenal ulcer patients required long-term therapy to maintain remission and control symptoms.\textsuperscript{50} As stated before the nowadays advised therapy of first choice in PUD patients is \textit{H. pylori} eradication.

Life-long therapy by GERD patients,, although very beneficial to relief symptoms, is questionable. The course of GERD shows that 40 \% of the patients with initial predominant reflux symptoms is not using ASD after 3 years and 50\% after 20 years, although patients were not always symptom free.\textsuperscript{51,52} Recent studies show that on demand therapies, whatever it means (like intercurrent ASD, low dosages of ASD daily) may be feasible in such patients.\textsuperscript{53,54} Furthermore it has become clear, that only the severity of perceived symptoms and the impact of symptoms on the quality of life and not the endoscopic abnormality in mild GERD has to be the goal for ASD treatment since no complications have to be expected in patients with this type of GERD.\textsuperscript{55,56}

In functional dyspeptic patients it has always been proposed to treat short-term, if necessary several times a year. In addition, it has to be noticed that among GERD and functional dyspepsia patients a considerable group of patients does benefit from placebo treatment or antacids.\textsuperscript{56} So, it might well be that a substantial proportion of patients is overtreated by long-term ASD treatment.

\textbf{Intervention groups}

- \textit{patients with peptic ulcer disease}
It is expected that patients with life-long recurrence of this disease would become permanently free of complaints and can finish ASD use after successful eradication of \textit{H. pylori}. However, it may well be that among these patients with PUD, patients with newly developed or a previous concomitant diagnosis of esophagitis may still require ASD despite successful \textit{H. pylori} eradication.\textsuperscript{57}

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\textbf{sub-aim 6}

* to study the impact of \textit{H. pylori} eradication on the dyspeptic course and use of acid suppressant drugs in patients with peptic ulcer disease (chapter 6)
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-H. pylori positive patients with non ulcer dyspepsia
In a test and treat approach all H. pylori positive dyspeptic patients are treated with an H. pylori eradication therapy. There is debate about whether successful eradication of H. pylori leads to the development or exacerbation of GERD due to the absence of acid buffering by H. pylori derived urease production.\textsuperscript{21,58,59} This may influence the use of ASD. H. pylori eradication studies in functional dyspeptic patients are far from uniform in their results on the effect of H. pylori eradication on relief of dyspeptic complaints and subsequent use of ASD. In some studies dyspepsia improved in a small number of patients after H. pylori eradication, in others no effect was observed at all.\textsuperscript{22,25}

**sub-aim 7**
* to evaluate the influence of H. pylori eradication on tapering maintenance doses of acid suppressant drugs in patients with chronic non-ulcer dyspepsia (chapter 7)

-H. pylori negative patients
In these patients, also comprising patients with GERD or functional dyspepsia it is questioned, whether a supported tapering by the GP including explanations of the endoscopic results more in detail, general measures relevant for the patient (like the role of coffee, alcohol, weight, smoking, stress, use of NSAIDs, possible rebound effects after withdrawal of ASD) and the 3 weeks of gradual reducing the ASD, is beneficial.

**sub-aim 8**
* to investigate the ability of tapering the use of acid suppressant drugs in H. pylori negative chronic dyspeptic patients on long-term use of acid suppressant drugs and the role of the general practitioner in this tapering process (chapter 8)

Finally, in the last chapter the findings of the various studies are discussed.

References


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