Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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General Discussion
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The main results of this thesis on tapering acid suppressant drugs (ASD) in chronic dyspeptic patients on long-term ASD in primary care are summarised. Furthermore selection of study patients, risk factors, medication use, methods of this study, practical implications and recommendations for management of dyspepsia in general practice and future research are discussed.

Main results

* Firstly, we have conducted an inventory study on long-term (>12 weeks per year) ASD use in general practice. We found that ASD were prescribed on a long-term basis in 922/46,813 patients (2%) in 24 general practices. It was questioned whether the use of ASD could be more (cost)effective by several interventions.

* Depression and phobia are not more common in chronic dyspeptic patients than in a control population, but anxiety among men is. It seems that these disorders are not well recognised by a GP. The health status of chronic dyspeptic patients is in all aspects worse than in a general population. This was mainly attributed to the patients with a selfreported psychiatric disorder. Fear of cancer was observed in half of the patients and even in half of patients with prior investigations. H. pylori was not related to the psychological disorders nor was it related to the health status of chronic dyspeptic patients.

* Performance of non-invasive tests to exclude ulcer disease in chronic dyspeptic patients depends on the ethnic composition of the patient population and the prevalence of ulcer disease. These tests require separate validation in primary care setting, before introduction. In natives younger than 55 years old with a negative ELISA test, gastroscopy can be prevented.

* In patients with ulcer disease 4 days H. pylori eradication regimen (omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg) showed to be highly efficacious (100% H. pylori eradication rate), well tolerated and as effective as same regimens of longer duration Even despite that in our population we had a moderately prevalent metronidazole resistance.

* Prevalence of CagA+ H. pylori and its relation with PUD is influenced by patient’s country of origin. Neither the presence of PUD, CagA status nor metronidazole resistance affected the effectiveness of a 7-day regimen consisting of omeprazole 20 mg, clarithromycin 250 mg and metronidazole 400 mg.
A primary care based cohort of patients with chronic dyspepsia taking long-term ASD was followed over 6 months next to a period of titration of ASD to zero over 3 weeks. Patients were asked to use antacids as first escape medication and ASD, if needed, on demand in low dosage. Over 50% of the patients could stop ASD consumption during 6 months. In all patients (n=360) the mean daily units of ASD per patient reduced from 2.04 at entry to 0.45 during follow-up, a 78% decrease (p<0.001). If patients restarted the use of ASD, 80% of them restarted in the first 8 weeks after the 3 weeks of titrating down the dose of ASD.

- In patients with documented peptic ulcer disease (PUD) (past or present), who received successful H. pylori eradication, a very striking reduction in ASD use (98%), with diminution of pre-existing reflux symptoms and only a small emergence of de novo reflux symptoms, was observed.

- In H. pylori positive patients without ulcer disease an important 78% reduction of use in ASD was observed unrelated to a successful H. pylori eradication. In a subgroup of patients with gastro esophageal reflux disease (GERD) H. pylori eradication was even disadvantageous for the use of ASD during follow-up.

- In H. pylori negative patients a reduction of 71% in ASD use was achieved. An ASD tapering strategy supported by the GP had no positive result on the proportion of patients that could withdraw the medication. However, it lead to a significant reduction in the amount of ASD use in patients who restarted ASD in comparison with ASD restarted patients not coached by their GP. It is noticed that it is more easy to stop ASD for patients who were endoscopy negative or who were initially on H2-receptor antagonists. It is harder to stop or to diminish ASD use for patients who had a diagnosis of esophagitis grade one (Savary/Miller)/hiatal hernia or who were on proton pump inhibitors at study entry.

**Chronic dyspepsia in general practice**

*Selection of study patients*

Of 54 general practices 2230 patients were using ASD on a long-term basis according to the pharmacy lists. After exclusion of 1147 patients for reasons of age (>85 years), cancer, use of NSAIDs, esophagitis grade 2-4, as the most important reason of exclusion, 49% (1083) of chronic dyspeptic patients met eligibility criteria; 434 (40%) of them volunteered to participate for endoscopy and 391 patients participated in the follow-up study. Main reason to refuse participation was anxiety for endoscopy. Only a minority of patients gave satisfaction with the actual use of ASD and thereby reluctance of tapering the use of ASD as reason for not willing to participate. In 360/391 chronic dyspeptic patients, ASD use was evaluated per
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In conclusion, for various study related reasons the proportion of included patients was about one-fifth of those originally long-term on ASD use.

Risk factors of dyspepsia

Psychological disorders and health status

Fifty three percentage of the dyspeptic patients were suffering (in the past) from depression, anxiety or phobia. Those psychiatric disorders were not that well recognised by the GPs, since only a small minority of patients had such a diagnosis mentioned in their GP’s files somewhere, although the majority of patients claimed to have sought help for such disorder. Possibly, GPs focussed too much on dyspeptic problems or these patients had difficulties presenting their psychological symptoms. In a recent study in the Netherlands among 850 dyspeptic patients consulting their GP for a first or new episode of dyspepsia, it was observed that psychosomatic features were discussed with only one-third of patients and that during the observed year only 10% of these patients were treated without medication.¹ The health status in dyspeptic patients was worse than in the general population. This was surprisingly not related to the stomach disorder, but to the psychiatric disorder. In general, not chronic dyspepsia but the reported psychological co-morbidity seems to make chronic dyspeptic patients assess their health in a negative light. Our population of chronic dyspeptic patients may be a selection of people more worried than others. The fact that about half of the patients had fear of cancer of the upper gastrointestinal tract is consistent with this notion. A similar rational for consulting behaviour has been observed in patients with irritable bowel syndrome.² This conception cannot easily be changed in many of the patients, since even half of the patients with investigations in the past still had such a belief at entry of this study. Since our study was designed as a case-control study and various potential confounders could not be taken into account we were not able to completely reveal the complex relationship between psychological disorders and dyspepsia.

H. pylori infection

We have shown, that ethnicity is a relevant issue in chronic dyspepsia in general practice. This is a new aspect in the management of dyspepsia in primary care, and given the high immigration rates in the western world a very relevant one. The high prevalence of *H. pylori* infection (almost 80%) among chronic dyspeptic patients long-term on ASD coming from *H. pylori* endemic areas makes various non-invasive test results unsuitable in this subgroup. In practice however, this aspect is often not considered. A critique may be that it seems
academic and perhaps even unethical to mix all immigrants from so many different countries together. However, in our study this finding was quite consistent over the various groups of immigrants. Both in young as in older dyspeptic immigrants the prevalence of *H. pylori* infection and CagA+ *H. pylori* was much higher than in natives.

Before introduction, non-invasive tests require validation in primary care setting in the population to which the tests will be applied, as we did. Since professionals with different background and experience will use such a test kit, ease in use is one of the most important aspects besides good test characteristics. The desktop test and breath test used, were for those reasons not ideal, although the breath test in itself had very good test characteristics. Talley et al had similar findings with an other office-based test that didn’t turned out to be very useful, if used in a primary care setting.³

*H. pylori* eradication therapies used in our study were highly effective, even the four days eradication treatment in PUD patients despite a moderately high prevalent metronidazole resistance, which is generally seen as a major cause of failure. Not many studies have been performed to explore the minimum duration of an *H. pylori* eradication therapy comparable to ours. Findings similar to our results have been reported for a five days treatment.⁴ Recent reviews on *H. pylori* eradication therapies show in general lower eradication rates in patients with metronidazole resistance.⁵ The number of patients in our treatment regimens might have been too small to reveal a statistically significant difference between *H. pylori* eradication therapy in patients infected with metronidazole resistant *H. pylori* and patients infected with metronidazole susceptible *H. pylori*.

Based on our findings in chronic dyspeptic patients long-term on ASD, *H. pylori* eradication is efficacious on ASD use only in patients with the diagnosis of PUD. We found that eradicating *H. pylori* in chronic dyspeptic patients with functional dyspepsia had no beneficial effect on the use of ASD. In patients with GERD, it had even an disadvantageous effect on ASD use which is in line with the hypothesis of Labenz that *H. pylori* may be a protective factor for GERD.⁶

Until now, there is no firm evidence in the literature for a causal relationship between *H. pylori* and functional dyspepsia nor GERD. There is still disagreement on whether *H. pylori* eradication decreases the symptoms of functional dyspepsia. Some studies found an improvement of symptoms, although very small, after successful eradication, while other studies found no convincing evidence that eradication of *H. pylori* is efficacious for relieve of symptoms in patients with functional dyspepsia.⁷-¹⁰
Medication use during follow-up

To our knowledge, no other primary care study has been conducted targeted reduction of the use of ASD. In general, medication studies in dyspepsia try to reveal a better performance of a certain drug in comparison with another drug in order to control dyspeptic symptoms or to control the severity of esophagitis in GERD. Our study shows that reduction of ASD use is feasible in long-term ASD users with PUD and non ulcer disease. About 50% of the patients abstained ASD and those who used ASD, used less. An almost 80% reduction in ASD use was observed.

Recent reports, confirm our findings of the feasibility of reduction of ASD use for chronic control of dyspeptic symptoms. Not every patient, who stopped ASD use, was symptom free. However, they could control their symptoms with low dose of cheaper escape antacids and thereby contribute to overall reduction in ASD use.

Methods of the study

Design
The study design is general practice based with methods commonly used in general practice. We have faced no problems in including GPs for the study. Probably due to the actuality of the subject and due to the fact that most of the time consuming work was performed by the principal investigator, GPs and their assistants were very willing to participate. It takes about one complete day per practice to investigate of all patients long-term on ASD the prior results of investigations and reasons of prescription. Since most of the GPs had this information not at short notice available, going back in the past correspondence of specialists was necessary in order to find out that in some patients the initial problem was a peptic ulcer disease. It is questionable whether a GP would do this time consuming job as thoroughly as the investigator in this study.

Randomisation for the H. pylori eradication medication and placebo treatment was conducted in a double blind fashion. The randomisation of the H. pylori negative patients was done according to a computerised randomisation list. Thus these randomisations were performed in a proper way.

For the psychological disorder study we had to use three different control populations. A single control group would have been better. However, this aspect of the thesis was foreseen in the initial design. We still think that this study adds further thinking about the relation between psychological factors and (presentation of) dyspeptic complaints in general practice.
The intervention by the GP was performed according to protocol, however, we do not know for sure how much efforts each GP has put in the tapering process. Since the number of participating GPs was rather high, we consider this part to be a good reflexion of what might be possible in daily practice.

We had no control group without intervention on the use of ASD and therefore we cannot say what the natural course and thereby the use of ASD would have been in patients with same inclusion criteria as we had. Nor have we, also due to resources restraints, been able to follow the excluded patients in the same manner as we did the included patients.

Patients
In this thesis we have focussed on patients with long-term use of ASD. Since in the Netherlands all patients are listed, pharmacy lists are very helpful to a GP in identifying long-term ASD users. An advantage in our study was that most of the participating GPs had only one (often on line) to three co-operating pharmacists. GPs in the city centre co-operating with many different pharmacists may face difficulties in identifying all patients.

The included patients, being 50% of all patients long-term on ASD in primary care, was a selected, rather healthy group of patients in comparison with the excluded patients. Of the eligible patients, 40% participated despite the burden of, in most cases, repeated endoscopy. We observed no selection bias regarding sex, but the mean age of the study population was a bit younger than non participating eligible patients, which could be expected. Furthermore, it might be that due to language problems, that immigrants were relatively under represented while due to the expectation of a possible curing treatment patients with a history of PUD were most likely over represented. Endoscopy was the great obstacle rather than prospects of reducing ASD use. Despite the fact that the other half on long-term ASD use were excluded, this does not mean that a reduction of ASD use in that group is not feasible.

Instruments
Since the gold standard was endoscopy with biopsies for detection of *H. pylori* infection our results on the endoscopic diagnosis and *H. pylori* status are valid. A critique may be that patients had stopped long-term ASD use one week before the endoscopy, which may have masked a diagnosis of ulcer disease or esophagitis. So, this in fact reflects daily clinical practice.

Since we had a good gold standard, the results of the study on the performance of the non-invasive tests are valid as well. The performance of the office-based *H. pylori* test may have been better than in daily practice, since the use of the test was explained by the principal investigator and practised by the GP assistant before actual use on patients. In many cases
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this exercise was definitely necessary.

Our symptom questionnaire for psychiatric disorders is not formally validated. However, it on face-value has a high concordance with the list of symptoms of the psychiatric diagnoses according the DSM-III-R. The COOP/Wonca charts have proven their value for assessment of functional health status in research and clinical practice at many different locations and are not time consuming and well accepted by the patients.

Outcome

Our follow-up period is rather short, however, long enough to avoid bias due to the placebo effect of the intervention and the endoscopy itself (the so-called "Hawthorn effect"). The outcome measures such as ASD use and antacids were objective and reflect the reality of daily clinical practice. We do not know whether patients may have taken over the counter medication. However, we think they would have reported this to us.

Practical implications and recommendations

Management of H. pylori

Most patients with dyspepsia are treated in primary care on the basis of symptomatology, with life style advice or drug prescription aimed at symptom control as main intervention. Only when there is no response or a relapse of symptoms further investigations are considered by the GP. Prompt endoscopy is not a common policy in primary care. The discovery of a causal relationship between PUD and infection by H. pylori brought a new aspect in the management of dyspepsia. Eradication of H. pylori in patients with PUD put an end to the relapsing nature of this disease and as observed in our study, to the need of ASD in almost all patients. In the euphoria of this discovery, treatment strategies were directed to a conversion into a ‘test and treat’ approach: as first step no more empirical treatments, but immediate testing for H. pylori infection and to treat if positive without endoscopy. However the majority of dyspeptic patients has no PUD. Even in the subgroup of young chronic uninvestigated H. pylori positive dyspeptic patients participating in our study the actual prevalence of PUD was rather low (20%). So, to 80% of H. pylori positive patients a blind H. pylori eradication therapy without an underlying diagnosis of PUD would have been given in such an approach. In general, these patients have functional dyspepsia or gastro esophageal reflux disease (symptomatic or erosive). As stated before, a minority may benefit of H. pylori eradication.
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It is not advisable to eradicate *H. pylori* in patients without peptic ulcer disease. In patients with peptic ulcer disease a 4 days eradication therapy is sufficient.

In chronic dyspeptic immigrants with a high prevalence of *H. pylori* infection and ulcer disease we recommend no serological or breath testing but endoscopy in all patients. We propose a test and scope approach in chronic dyspeptic native patients: Testing for *H. pylori* infection in native patients < 55 years at the moment that the GP considers, after (several) empirical treatments, further investigation and performing an endoscopy only in *H. pylori* positive patients. This will diminish the number of endoscopies to be performed.

Test and treat strategy is not recommended.
All dyspeptic immigrants on long-term ASD use should have an endoscopy.
There is no need for endoscopy in *H. pylori* negative dyspeptic natives younger than 55 years.

Only if PUD is diagnosed an eradication therapy should be given.

Some remarks can be made about such an approach. Treatment of proton pump inhibitors (PPIs) aggravates *H. pylori* gastritis in the corpus, but improves it in the antrum. As corpus gastritis seems to be associated with elevated carcinogenic risk, it is for this reason suggested to consider prophylactic *H. pylori* eradication therapy before initiating long-term PPI therapy.\(^\text{15}\) Secondly, absence of PUD at the moment of endoscopy is no guarantee for a PUD free future. In our study 11% (3/28) of investigated *H. pylori* positive patients without a diagnosis of PUD, had a PUD diagnosed at entry endoscopy. In some recent studies it is stated that *H. pylori* eradication (test and treat) is a cost-effective option, which should be preferred above empirical treatments with antacids and investigations.\(^\text{16,17}\) However, moment of screening for *H. pylori* infection, costs of drugs and investigations, prevalence of *H. pylori* infection and PUD may differ between patient populations in different countries and even between different clinical settings in the same country.

Our results should encourage GPs to identify patients with a history of PUD among patients long-term on ASD. As shown in our study, pharmacy lists of prescribed ASD are helpful in the identification process.

Our approach of encouraging chronic dyspeptic patients to stop ASD use or reduce them in a gradual way, using antacids as first escape medication and if necessary using ASD on demand in low dosage, may lead to a more cost effective option than *H. pylori* eradication in these patients.

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Long-term use of ASD

In the current Dutch GP guidelines it is stated that long-term use or maintenance use of ASD could be initiated in patients with several relapses of functional dyspepsia or GERD and to attempt to stop ASD annually. In our study we have challenged this duration of therapy in order to control disease. Furthermore, the guidelines provide no guidance on how to instruct the patient to stop the ASD. Therefore, we recommend in a future revision to adapt the guidelines on these aspects.

Results presented in this thesis demonstrate, that reduction of ASD use is feasible in patients with ulcer and non-ulcer disease who are on long-term use of ASD. Patients should be told to stop ASD or to reduce ASD in a gradual way, to use antacids as escape medication and if needed ASD on demand in low dosage.

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<th>Chronic use of ASD can be reduced by</th>
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<td>simply asking the patient to stop</td>
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<td>stopping gradually in three weeks</td>
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<tr>
<td>using antacids if necessary</td>
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<td>in patients with severe symptoms using ASD on demand</td>
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Furthermore, psychological problems should be explored and patients should be told that no serious disease is responsible for their symptoms.

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<th>More attention to psychiatric disorders in patients long-term on ASD use might be helpful</th>
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<td>More attention to the fear of cancer in patients long-term on ASD use might be helpful</td>
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In that way control of dyspeptic symptoms is returned to patients, after some initial guidance: if the physician leaves decisions to use escape antacids, to taper - , to discontinue - , to restart - or to change the dosage of ASD to the patient, according to the severity of symptoms. Also these recommendations need implementation in the guidelines and practice.

Future research recommendations.

The study design is general practice based with methods that may encourage the individual GP to start a similar project among patients on long-term use of ASD. Therefore the first recommendation should be of course a proposal to do a same kind of project conducted by the GPs themselves, in order to see whether our good results could be repeated when implemented in daily practice.
Future studies and further analysis of our data may reveal a combination of variables (such as smoking, psychological comorbidity, \textit{H. pylori} status, CagA status, type of dyspeptic symptoms) to predict PUD with a higher chance than the prior chance of 20\%, being the prevalence of PUD among \textit{H. pylori} positive chronic dyspeptic patients.

We wonder, whether paying attention to the fears of patients and psychiatric disorders will contribute to actual improvement in the health of chronic dyspeptic patients on long-term ASD and may thereby perhaps be a better option than the mere prescription of ASD on a long-term basis. Future prospective studies with a long-term follow-up may give an answer whether the chronic illness leads to psychological disorders, or that worries or psychological disorders generate and influence dyspeptic symptoms perceived by patients.

In general, restart of ASD took place in the first 8 weeks after the 3 weeks of titrating down the dose of ASD. Further analyses are needed to investigate which determinants are responsible for this observation. Rebound acid hypersecretion, which is observed in healthy subjects after treatment with \textit{H}_{2}-receptor antagonists or PPIs may lead to relapse of dyspeptic symptoms. We were unable to draw conclusions about the effect of rebound acid hypersecretion on the restart of ASD use, since this was not tested in our study.

Furthermore, for \textit{H. pylori} negative patients who were endoscopy negative it was more easy to abstain from ASD than for patients with a diagnosis of esophagitis grade one / hiatal hernia. In addition, of patients initially on proton pump inhibitors less stopped ASD than of patients on H\textsubscript{2}-receptor antagonist at study entry. These observations may be indicative of increased esophageal acid exposure in these patients due to rebound acid hypersecretion, which is observed after withdrawal of long-term treatment with ASD. It might well be that prescription pattern of physicians in a subset of dyspeptic patients induce the dependence of maintenance ASD therapy. Our findings underline the importance of a well considered selection of sort, dosages and duration of ASD therapy. Future drug research should not only be focussed on the short-term effects of medication but also on the possible long-term implications.

\textbf{references}

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