Chronic dyspepsia in general practice. Tapering the use of acid suppressant drugs
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Chapter 1

A population-based analysis of long-term acid suppressant drug use in 24 general practices in the Netherlands

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Background
A considerable proportion of the medication budget of the Dutch general practitioners is spent on long-term prescribed acid suppressant drugs. The magnitude of long-term prescription of acid suppressant drugs in general practice, the diagnosis and the frequency and means of confirming the primary working diagnosis were investigated.

Methods
Retrospective descriptive study in 24 general practices in the Amsterdam region. Patients receiving long-term acid suppressant therapy (≥12 weeks/year) were identified from a total of 46,813 patients by extracting data from computerized medication databases of pharmacies. The magnitude, type of medication, indications for prescription and investigations performed were analysed.

Results
922/46,813 patients (2%) received long-term acid suppressant therapy. The mean duration of prescription was 33 weeks. The duration of prescription varied from 12 weeks in 8% of the patients to ≥52 weeks in 23% of the patients. In 25% of the patients no investigations were performed, whereas in 75% endoscopy or a barium meal was done. The predominant diagnoses in investigated patients were ulcer disease (39%), GERD (49%) and functional dyspepsia (18%). *H. pylori* status was available in 29% of patients with ulcer disease. Eradication therapy was reported in 44% of these patients.

Conclusions
In general practice in the Amsterdam region 2% of patients used long-term acid suppressants. Patients with ulcer disease may stop acid suppressants after apparent successful *H. pylori* eradication. Uninvestigated patients require additional proof of underlying disease, *H. pylori* status and subsequent treatment approach. Development of tapering strategies in patients with mild reflux disease or functional dyspepsia is required.
**Introduction**

In general practice, patients suffering from symptoms such as stomach-ache, heartburn, nausea and abdominal pain are common. The average Dutch general practice includes around 2350 patients of whom 2-3 patients will visit their general practitioner for dyspepsia weekly. Treatment of dyspepsia according to the guidelines of the Dutch College of General Practitioners (DCGP) is directed towards symptom relief, usually on an empirical basis, except for those with alarm symptoms, who are referred for endoscopy. Medication is prescribed in a stepwise fashion from less potent antacids and prokinetics to the more potent H2-blockers and proton pump inhibitors. During this study, long-term treatment with acid suppressant drugs (ASD) was, according to the DCGP-guidelines, only indicated for relapsing ulcers or ulcer-like complaints, relapsing esophagitis and relapsing gastroesophageal reflux-like symptoms.

ASD belong to the group of drugs that represents the highest expense in the medication budget of the Dutch general practitioners (GPs) because of the high cost of these drugs, the high frequency of prescription and particularly the prescription on a long-term basis. Therefore the question is justified whether the indication for prescribing ASD was always appropriate.

The aim of this study was to elucidate the background for long-term prescription of ASD in general practice. Both the magnitude and the duration of long-term prescription of ASD therapy, was investigated. In addition, the initial working diagnosis, the diagnostics performed to confirm the working hypothesis and the final diagnosis have been evaluated.

**Methods**

**Patients**

In this descriptive study, data from patients using long-term acid suppressant drugs were collected retrospectively in 24 general practices in Amsterdam, over the period September 1994 - August 1995.

*drugs selected for this study were those listed in the 'National Dutch Pharmacotherapeutical Compass 1995 under the chapter entitled 'drugs influencing peptic diseases' with antacids, mucosa-protective agents, prokinetics, H2-blockers and protonpump inhibitors as the main groups.' Long-term prescription was defined as 'use of ASD for more than twelve weeks during the previous year'. Patients were identified by means of computerized medication data obtained from all pharmacists cooperating with the participating GPs. Name, age, sex, type of medication, dosage and duration of prescription, use of possible risk-bearing co-medication (aspirin, NSAIDs and/or prednisone for more than six weeks during the research year) were extracted from the computerized files of the pharmacists by the principal investigator (G.H.). In the Netherlands, National Health (Service) patients are registered at one pharmacy and can get their medication only at this pharmacy. Patients with a private
health insurance usually get their medication at only one pharmacy as well. This way and due
to the fact that most of the participating GPs prescribed online with the pharmacists, almost
all patients from the participating general practices who received long-term treatment with
ASD could be identified.

**Confirmation of gastrointestinal diagnosis.**
In the Netherlands, GPs receive all available medical information on their patients (i.e. letters
from specialists, results from any examination performed) and stores this information in the
patient’s medical history file. When a patient moves or switches to another GP the entire
medical history is sent to the new GP. With the use of this medical history file in the GP’s
office, information on all patients included into this study was collected by the principal
investigator (G.H.) in order to determine the diagnosis/reason for prescription and the
investigations (including *H. pylori* investigations) which had been undertaken to confirm that
working diagnosis. Gastroscopy or barium meal X-ray at any time during a patient’s life was
considered to be the investigation for confirmation. If the prescription started following or as
a consequence of this investigation it was considered to be the reason for initiating the current
long-term treatment. Verification and completion of the obtained data took place in a face to
face evaluation between the principal investigator of this study (G.H.) and the GP of the
patients involved.

**Analysis and Statistics**
Patients were categorised into group A or B. In group A investigations to confirm a working
diagnosis were performed; in group B no (additional) investigations were performed. Three
patient subgroups were identified within group A having ulcer disease (AI), gastroesophageal
reflux diseases (AII) or functional dyspepsia (AIII).

In group AI ‘ulcer disease’, all patients with a duodenal ulcer, gastric ulcer or nonspecified
ulcer were included. In group AII ‘gastroesophageal reflux disease’ (symptomatic or erosive)
were categorised. In group AIII ‘functional dyspepsia’, patients were classified with gastritis
or no imaging abnormalities. Patients without a confirmed diagnosis were placed under
uninvestigated ‘stomach complaints’ (group B). Patients with an ulcer and esophagitis were
placed under group AI for their patient characteristics and medication prescription and under
both group AI and AII for their medication indication, diagnostic tests and eradication of *H.
pylori*.

Data were analysed with the use of SPSS software (version 7.5.3). The Chi-square test was
used for comparison of proportions. Significance was set at $\alpha = 0.05$ (two-sided).
Results

General characteristics and medication prescription
Of 46,813 patients of the registered list size of the practices, 988 (2.1%) were identified as long-term users of ASD. Of these 988 patients, 66 were excluded because of acid suppressant drug use for gastric- or esophageal cancer or non-gastric-related indications like renal failure, or discontinuation of visits to the GP (moved or temporary visitor). The demographic and prescription characteristics of the remaining 922 patients are presented in table 1.

Group AI consisted of 271 ulcer patients; group AII of 294 patients with reflux disease; group AIII of 127 patients with functional dyspepsia and group B consisted of 230 patients without investigations.

The mean age of the participants was 61 years (SD 17 years; range 15-102 years). Among the long-term users, long-term treatment was significantly (p<0.05) more frequently prescribed for women compared to men (55% and 45%). In group AI (ulcer group) significantly (p<0.05) more men than women used long-term treatment (59% and 41%, respectively).

Overall ranitidine was the drug most commonly prescribed, followed by omeprazole and cimetidine. For patients in the reflux group (group AII) omeprazole was most commonly prescribed, followed by ranitidine and cimetidine. The mean duration of prescription was 33 weeks in the year of study, with the highest mean duration in group AII 'reflux disease' (38 weeks). Almost a quarter of all patients (23%) had been using these drugs for more than one year. In more than half of all patients (53%) the medication was prescribed for one episode, in the others for two or more episodes (i.e. intermittent prescription).

During the study period, 154 patients (17%) had used potential risk bearing co-medication for more than six weeks. Almost one-third of the risk bearing co-medication users (48 patients) belonged to group AI (data not shown).

Confirmation of working diagnosis
In 692 of the 922 (75%) patients diagnostics were performed to confirm the primary working diagnosis. In 519 of these 692 patients (75%) a gastroscopy was performed and in 138/692 (20%) a barium meal X-ray. In 35 patients (among whom 15 with a stomach perforation or ulcer bleeding) the specific form of investigation was unclear. Of the 692 patients, 271 (39%) belonged to group AI (ulcer diseases); 342 (49%) to group AII (gastroesophageal reflux disease) and 127 (18%) to group AIII (functional dyspepsia).
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Table 1. Characteristics and prescriptions in 922 patients (%) with long-term acid suppressant drug prescription in 24 general practices in the region of Amsterdam.

<table>
<thead>
<tr>
<th>Patients</th>
<th></th>
<th>Diagnosis after investigation</th>
<th>Group B: stomach complaints without investigation (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total (n=922)</td>
<td>group AI: ulcer disease* (n=271)</td>
<td>group All: gastroesophageal reflux disease** (n=294)</td>
</tr>
<tr>
<td>female</td>
<td>511(55) 41%</td>
<td>41(52) 115(39)</td>
<td>70(55)</td>
</tr>
<tr>
<td>15-44 years</td>
<td>169(18) 11%</td>
<td>82(30) 48(16)</td>
<td>39(31)</td>
</tr>
<tr>
<td>mean age</td>
<td>61 63</td>
<td>63</td>
<td>57</td>
</tr>
<tr>
<td>Prescriptions</td>
<td>medication****</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ranitidine</td>
<td>442(48)</td>
<td>141(52) 115(39)</td>
<td>70(55)</td>
</tr>
<tr>
<td>cimetidine</td>
<td>236(26) 82(30)</td>
<td>48(16)</td>
<td>39(31)</td>
</tr>
<tr>
<td>omeprazole</td>
<td>241(26) 63(23)</td>
<td>130(44)</td>
<td>22(17)</td>
</tr>
<tr>
<td>famotidine</td>
<td>43(5) 16(6)</td>
<td>15(5)</td>
<td>4(3)</td>
</tr>
<tr>
<td>lansoprazole</td>
<td>13(1) 3(1)</td>
<td>5(2)</td>
<td>5(4)</td>
</tr>
<tr>
<td>antacids</td>
<td>140(15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-19 weeks</td>
<td>231(25) 67(25)</td>
<td>44(15)</td>
<td>44(35)</td>
</tr>
<tr>
<td>20-29 weeks</td>
<td>184(20) 56(21)</td>
<td>46(16)</td>
<td>27(21)</td>
</tr>
<tr>
<td>30-39 weeks</td>
<td>148(16) 40(15)</td>
<td>50(17)</td>
<td>22(17)</td>
</tr>
<tr>
<td>40-51 weeks</td>
<td>143(16) 44(16)</td>
<td>60(20)</td>
<td>15(12)</td>
</tr>
<tr>
<td>&gt;52 weeks</td>
<td>216(23) 64(24)</td>
<td>94(32)</td>
<td>19(15)</td>
</tr>
<tr>
<td>Mean prescription (weeks)</td>
<td>33</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Episodes of prescription (no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>485(53) 144(53)</td>
<td>179(61)</td>
<td>51(40)</td>
</tr>
<tr>
<td>2</td>
<td>271(29) 78(29)</td>
<td>81(28)</td>
<td>48(38)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>166(18) 49(18)</td>
<td>34(12)</td>
<td>28(22)</td>
</tr>
</tbody>
</table>

* duodenal ulcer and/or gastric ulcer; 48 patients had ulcer and esophagitis
** gastroesophageal reflux disease (symptomatic or erosive)
*** gastritis or normal aspect in endoscopy or barium meal
**** total is more than 100% because of prescription of more than one type of medication/patient, very sporadic
prescribed medication is not mentioned
The specific diagnoses of the subgroups are mentioned in table 2. In group AI, use of NSAIDs or prednisone was mentioned as the cause of the ulcer in 26/271 (9.6%) patients. In 29/342 (8.4%) patients in group AII a Barrett esophagus was diagnosed. In about 50% of the total number of patients the investigation had been performed more than five years ago. Each patient had been treated accordingly during the subsequent years.

Table 2. Indications for long-term (≥12 weeks) prescription of acid suppressant drugs to 922 patients (%) in 24 general practices in the region of Amsterdam.

<table>
<thead>
<tr>
<th>Indications</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Diagnosis after investigation</td>
<td>692 (75)</td>
</tr>
<tr>
<td>A I Ulcer disease*</td>
<td>271 (29)</td>
</tr>
<tr>
<td>duodenal ulcer</td>
<td>196 (21)</td>
</tr>
<tr>
<td>duodenal and gastric ulcer</td>
<td>17 (2)</td>
</tr>
<tr>
<td>gastric ulcer</td>
<td>43 (5)</td>
</tr>
<tr>
<td>nonspecified ulcer</td>
<td>15 (2)</td>
</tr>
<tr>
<td>AII Reflux disease</td>
<td>342 (37)</td>
</tr>
<tr>
<td>esophagitis and ulcer*</td>
<td>48 (5)</td>
</tr>
<tr>
<td>esophagitis</td>
<td>116 (13)</td>
</tr>
<tr>
<td>esophagitis and hiatal hernia</td>
<td>101 (11)</td>
</tr>
<tr>
<td>symptomatic</td>
<td>77 (8)</td>
</tr>
<tr>
<td>AIII Functional Dyspepsia</td>
<td>127 (14)</td>
</tr>
<tr>
<td>B: Stomach complaints without investigation</td>
<td>230 (25)</td>
</tr>
<tr>
<td>preventive</td>
<td>45 (5)</td>
</tr>
<tr>
<td>non-specific stomach complaints</td>
<td>146 (16)</td>
</tr>
<tr>
<td>reflux-like complaints</td>
<td>27 (3)</td>
</tr>
<tr>
<td>ulcer-like complaints</td>
<td>6 (1)</td>
</tr>
<tr>
<td>motility-like complaints</td>
<td>6 (1)</td>
</tr>
</tbody>
</table>

* 48 patients with esophagitis and ulcer disease are mentioned in A I and A II

In 230 of the 922 patients (25%) no investigations (group B), were performed. The working diagnoses which resulted in medication prescription are also mentioned in table 2. 'Non-specific stomach complaints' (i.e. dyspeptic symptoms that are not predominant reflux- or ulcerlike) was the most common indication (63%) in group B. Of 147/692 patients (21%) H. pylori status was evaluated. In most of these cases the correspondence between the hospital staff and the GP did not mention the current H. pylori status. In addition it remained
unknown whether eradication therapy was administered with or without successful eradication of the microorganism. (table 3)

Table 3. H. pylori diagnostics and eradication therapy prescriptions in 692 investigated patients with long-term (>12 weeks) prescription of acid suppressant drugs in 24 general practices in the region of Amsterdam (row percentages)*

<table>
<thead>
<tr>
<th>diagnosis**</th>
<th>H. pylori diagnostics</th>
<th>H. pylori-eradication therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI: ulcer disease (n=271)</td>
<td>78 (29)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>AII: reflux disease (n=342)</td>
<td>34 (10)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>AIII: functional dyspepsia (n=127)</td>
<td>35 (28)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

* the current H. pylori status, prescription and success of eradication therapy was often remained unknown
** 48 patients with esophagitis and ulcer disease are mentioned in A1 and AII

Discussion
In our study, 2% (922/46,813) of the patients used ASD for more than three months in the year of study and 0.8% for more than six months within that year.

Data from other studies, although not entirely comparable to ours, give an impression of the magnitude of long-term ASD prescription in other countries. In London, 0.8% of the general practice population (492/60,148) used ASD for more than six months continuously, which as in our study. In one-third of these patients an history of ulcer disease was mentioned. In Dundee, 4.4% of patients in six general practices (697/15,495) were mentioned on the authorization list to receive maintenance therapy. Many had a history of confirmed ulcer disease (27%), esophagitis (23%) or both (6%). Investigations in 23% of all patients revealed gastritis, duodenitis, hiatal hernia or normal aspect.

A disadvantage of retrospective research in general practice (and in general) is the vast difference in the completeness of registration of diagnoses and the availability of information from specialists among general practitioners. However, since verification and completion of the data, obtained from computerized prescription lists of pharmacies, patient files, a patient’s list of problems and letters from specialists took place face to face between the investigator of this study and the general practitioner, we consider the data to be complete and reliable.

In our study ASD was used continuously by almost a quarter of patients of all groups for more than a year and prolongation of the prescription was based on diagnostics usually performed years before. According to the guidelines that were in use during the course of this study the reason for being on maintenance ASD was justified for most patients. H. pylori diagnostics were only performed in a minority of the patients.

The major change in the most recent version of the guidelines of the Dutch College of General Practitioners (1996), is the role of H. pylori infection. Patients with duodenal ulcer (active or inactive), not caused by NSAID-use, should be treated with H. pylori eradication
therapy. Patients with an history of gastric ulcers need to undergo an endoscopy plus biopsies to exclude a carcinoma and to assess the *H. pylori* status with subsequent eradication therapy if positive. In principle, long-term ASD use is not necessary after successful eradication of *H. pylori* since the ulcer is not likely to relapse. However, patients with a concomitant diagnosis of esophagitis may require maintenance therapy despite successful *H. pylori* eradication. It is the task of the GP to identify patients with a history of ulcer disease and to eradicate *H. pylori*. With the help of computerized prescription data and the patient’s history file, patients with an history of ulcer disease can easily be identified. In the Netherlands, the practical implementation is still an important issue. Many of these patients are ‘invisible’ for the GP since they are treated with routinely repeated prescriptions without further consultation and therefore not treated yet for *H. pylori*.

The current Dutch guidelines do not advice to test for *H. pylori* in patients with GERD or functional dyspepsia. This is in line with guidelines developed with a primary care perspective and is in contrast, in fundamental ways, from those formulated by specialists. The role of *H. pylori* in esophagitis and reflux disease is not clear. There is debate about whether successful eradication of *H. pylori* leads to exacerbation of esophagitis due to the absence of acid buffering by *H. pylori* derived urease production. In our study one third of the patients suffered from gastroesophageal reflux disease which is easy to control but not to cure and may often relapse after tapering of ASD. An intermittent treatment on demand with ASD might be an effective approach in managing the complaints of a part of the patients with uncomplicated gastro-esophageal reflux disease and in reducing 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 patient dyspeptic complaints. In some studies dyspepsia improved after *H. pylori* eradication, in others no effect was observed at all. In general, no benefit is obtained. In these patients with functional dyspepsia, it may be sensible to try out a gradual tapering of ASD supported by antacid use, further exploration on psychosocial distress and advices on life-style improvement.

In the remaining 25% of the patients long-term medication was prescribed as a preventive measure or to patients without investigations. The guidelines advice further investigation after several empirical treatments and before patients are prescribed long-term ASD. Anxiety for endoscopy is one of the reasons for not having a confirmed working diagnosis. A small part of the anxious patients might benefit in a test and treat approach for *H. pylori* infection since they have an underlying ulcer disease. However, serology will not differentiate between either *H. pylori* infection at present or in the past and between ulcer or non-ulcer disease.

Use of ASD, especially proton-pump inhibitors, is becoming much more common. Physicians experience often a fast relapse of symptoms after discontinuation of therapy that may be related to rebound acid hypersecretion. The severity of rebound acid
hypersecretion seems to be related to the degree of elevation of pH level during treatment.\textsuperscript{23} It has been described that the pH in general is more elevated by PPI treatment than by H\textsubscript{2}R-antagonists.\textsuperscript{24} These findings underline the importance of a well considered selection of sort, dosages and duration of ASD therapy. It might well be that the prescription pattern of physicians in a subset of dyspeptic patients, especially in those with acid related dyspepsia, induce the dependence of long-term therapy.

Further profiling of the individual dyspeptic patient is needed in order to start a more adequate diagnostic strategy and to be able to start a tailor-made therapy. Research is warranted to develop strategies in tapering of acid suppressants in chronic dyspeptic patients in general practice.

References


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