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Strategies for discontinuation of proton pump inhibitors: a systematic review

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Abstract

Purpose. Proton pump inhibitors (PPIs) are considered to be overprescribed. Consensus on how to attempt discontinuation is, however, lacking. We therefore conducted a systematic review of clinical studies on discontinuation of PPIs.

Methods. Systematic review based on clinical studies investigating discontinuation strategies and discontinuation rates for users of antisecretory medication judged eligible for withdrawal. The databases Medline, Embase and Cochrane Library were searched to December 2013 using the terms antisecretory, anti-ulcer, PPI, acid suppressant, discontinuation, step-down, step down, cessation, tapering, withdrawal and withhold. Search terms were used either singularly or in combination. Papers written in English or Scandinavian were included. Concurrent hand searching was undertaken to pursue references of references. The website ClinicalTrials.gov was searched for unpublished results and ongoing studies. A total of 371 abstracts were scrutinized to determine relevancy.

Results. The thorough search resulted in six clinical studies on strategies for discontinuation of PPIs. All discontinuation regimens used in the studies differed, and several interventions have been tested in order to decrease use of PPIs. Discontinuations were reported across all studies ranging from 14% to 64% without deteriorating symptom control. Tapering seems to be a more effective discontinuation strategy than abrupt discontinuation.

Conclusion. Discontinuation of PPIs is feasible in a clinical setting, and a substantial number of the patients treated without a clear indication can safely reduce or discontinue treatment. Tapering seems to be the most effective way of doing this.

Key words: Dyspepsia, general practice, patient-centred care, placebos, proton pump inhibitors, withholding treatment.

Introduction

Prescribing of antisecretory medication, primarily proton pump inhibitors (PPIs), has increased substantially during the past decade (1). The rising use of antisecretory treatment is primarily due to increasing long-term use. Long-term use of PPIs is indicated as ulcer prophylaxis to patients at risk of peptic ulcer complications and treatment and prevention of relapse of reflux oesophagitis. Patients with frequent symptoms of gastrooesophageal reflux disease (GORD) might also need long-term treatment for symptom control. However, PPIs are considered to be overprescribed and a noticeable amount could be saved in health care budgets by reducing unnecessary prescribing (2).

PPIs were thought to have a low incidence of side effects, but evidence has cumulated to indicate that long-term use might not be as harmless as first considered, with concerns about possible adverse side effects, such as hypomagnesaemia and increased fracture risk, and drug interactions raised (3). In addition, previous studies have shown that as little as a few weeks of PPI treatment can cause hypergastrinemia, rebound acid hypersecretion and occurrence of acid-related symptoms in

previous asymptomatic individuals when the PPI is withdrawn abruptly (4).

Empirical antisecretory treatment is often used in general practice for management of uninvestigated dyspepsia, despite guidelines stating that the *Helicobacter pylori* test-and-treat strategy is more cost effective (5). Furthermore, it is known that there is a significant placebo response when treating dyspepsia, and that dyspepsia as a symptom is fluctuating (6). Hence, initiating empirical antisecretory treatment for an uncertain indication for more than a few weeks may lead to unnecessary long-term use. Patients with ambiguous symptoms that are not truly acid-related may develop truly acid-related symptoms, when discontinuing antisecretory treatment, necessitating continuous PPI treatment.

Qualitative research has shown that patients are quite receptive to making changes to their antisecretory medication (7). However, there is lack of guidelines or international consensus on how best to attempt PPI discontinuation and to decrease excessive or unnecessary use. We therefore conducted a systematic review of clinical studies investigating discontinuation strategies and their effect on discontinuation rates in patients treated with PPIs.

Methods

The literature databases Medline, Embase and Cochrane Library were searched by the first author assisted by a research librarian to December 2013 (no lower time limit) using the terms antisecretory, anti-ulcer, PPI, acid suppressant, discontinuation, step-down, step down, cessation, tapering, withdrawal and withhold. Search terms were used either singularly or in combination. Only papers written in English or Scandinavian languages and based on adult patients (aged 18 years or above) were included. Concurrent hand searching of relevant journals and article searches was undertaken for other possible references and to pursue references of references. The website recording trial information ClinicalTrials.gov was searched in a similar way for unpublished results of studies ('grey literature') and ongoing studies on the subject. Each unique abstract was scrutinized to determine relevancy by the first author. The complete list of included and excluded studies was checked by the rest of the authors. Any doubts regarding eligibility of a study were resolved through consensus among the authors. Two of the authors (JMH and DEJ) have several years of experience within the field of research of gastroenterology in primary care and to their knowledge all eligible studies were identified.

Data extraction was done by the first author and afterwards controlled by the author group. Any disagreements were solved through consensus.

The literature search and reporting of included and excluded studies was guided by the PRISMA 2009 Checklist and AMSTAR checklist for systematic reviews. Clinical studies investigating discontinuation strategies and the effect of an intervention on discontinuation rates in patients treated with PPIs were included.

Results

The literature search identified 371 studies. Of these, six clinical studies evaluating strategies for withdrawing PPIs met eligibility criteria (Fig. 1). One of the six studies was unpublished and found only through ClinicalTrials.gov. No ongoing studies were reported on this website.

Design, methods, number of patients enrolled, discontinuation rates and other characteristics of the six studies are listed in Table 1.

The most recent study by Murie *et al.* (8) included 157 patients with a diagnosis of GORD or non-ulcer dyspepsia (NUD). The patients were identified in a general medical practice in rural Scotland. Patients were considered eligible if they had been prescribed PPIs for a minimum of two consecutive months. This criterion was applicable for 15.2% of the total practice population. The included patients had a mean age of 63 years (32–89) and 55% of them were female. Approximately 25% were current smokers and 3% consumed alcohol above the recommend limit. A total of 23% had a normal body mass index (BMI) (18.5–24.9) with the rest being overweight/obese.

The patients attended a nurse-led dyspepsia clinic, where they were screened for *H. pylori* infection and treated if tested positive. Written and verbal information about dyspepsia, lifestyle and alternative treatment options was given to the patients. The nurse helped them formulate individual action plans to reduce

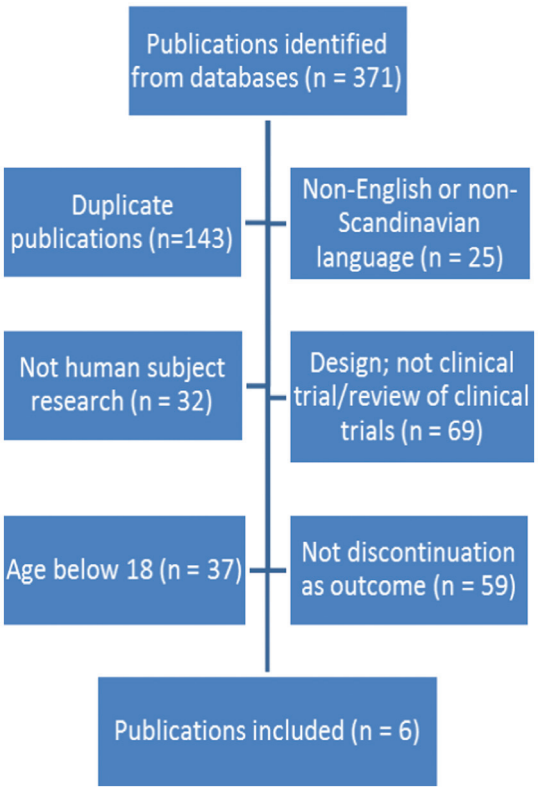

Figure 1. Flow chart of study selection.

Table 1. Characteristics of included studies

Study details					Intervention details		
Reference	Setting	Study design	*N* patients	Indication	Intervention	Follow-up	Discontinuation rate
Murie *et al.* (2012) (8)	Scotland	Non-RCT	157	GORD/NUD	Patient education	3 months	64% discontinuation 30% dose reduction
						12 months	34% discontinuation 50% dose reduction
Krol *et al.* (2004) (9)	The Netherlands	RCT	113	Unknown	Information letter from GP	12 weeks	24% vs. 7% (RR = 3.56)
						20 weeks	22% vs. 7% (RR = 3.25, ns)
Björnsson *et al.* (2006) (10)	Sweden	Double-blinded RCT	97	GORD/NUD	Endoscopy, tapering vs. omeprazole	12 months	31% vs. 22% (ns)
Zwisler (2008) (11)	Denmark	Double-blinded RCT	171	GORD/NUD	Esomeprazole 40 mg vs. placebo	12 months	28%
Reimer *et al.* (2009) (4)	Denmark	Non-RCT	78	Unknown	Abrupt withdrawal	6 months	14%
Inadomi *et al.* (2001) (13)	USA	Non-RCT	71	GORD	Step-down	12 months	58%[a]

Description of all studies included (n = 6). Non-RCT, non-randomized, non-comparative study; ns, statistically non-significant.
[a]30/41 (73%) of the patients still needed H2RA and/or prokinetics.

or stop PPIs. Participants were also offered a prescription for an alginate for rebound or breakthrough symptoms. The primary outcome was the proportion of patients being able to step down or off PPIs. At a 3-month follow-up, 64% of the patients were off PPIs and 30% had reduced their dosage. At a 12-month follow-up, 34% remained off PPIs and 50% were on reduced dosage compared to their dosage prior to study inclusion.

There were no significant differences between patients who successfully reduced or discontinued PPI and those that reverted for the variables gender, age, smoking status, alcohol use or BMI.

In the Dutch study by Krol *et al.* (9), 20 GPs used their medical record system to each randomly identify eight patients who had been prescribed PPI for at least 12 weeks. The GPs were randomized to either sending a simple information leaflet to the selected patients, giving information about dyspepsia, updated guidelines and encouraging them to consult their GP about further treatment (intervention group), or giving usual care/no intervention (control group). All patients received questionnaires at baseline and follow-up. The questionnaires included items regarding symptom severity, quality of life and patient characteristics. The primary outcome was the proportion of patients having stopped or reduced PPI use or reduced their prescription dose, assessed at 12 and 20 weeks after the intervention. At the 12-week follow-up, 24% (14/59) in the intervention group had stopped or reduced their use of PPIs compared to 7% (3/45) in the control group [risk ratio (RR) = 3.56, 95% confidence interval (CI): 1.09–11.64] without a decrease in symptom control or quality of life. The difference persisted but not statistically significant at the 20-week follow-up (22% vs. 7%, RR = 3.25, 95% CI: 0.98–10.83).

Half of the patients included had high educational level and 60% were female. Most of them had had dyspepsia complaints for >1 year and the majority had daily use of PPI. More than half of the patients had been referred to a specialist due to their symptoms. There were no significant differences regarding patient characteristics between the experimental group and the control group.

Only 10% of all patients stated in the baseline questionnaire that their GP had discussed when to stop using PPIs. Although patients with oesophagitis grade C or D were excluded, 18% were on double standard dose of PPI per day. In the Swedish study by Björnsson *et al.* (10), individuals collecting a prescription for a PPI at the pharmacy were consecutively invited to participate in a study investigating the possibility of discontinuation of PPIs. A total of 286/307 (93%) fulfilled the inclusion criteria of using PPIs for >8 weeks and not having a history of peptic ulcer or oesophagitis. A total of 116/286 (40%) agreed to participate and filled in a questionnaire about patient characteristics. A total of 54% were female and had been treated with PPIs for several months ranging from 4 to 180 months. Half of the patients were on omeprazole, and 61% (59) of the total cohort had previously had an endoscopy performed.

All of the patients agreeing to participate had a gastroscopy performed. At endoscopy, 19/116 (16%) were excluded due to findings of oesophagitis (16/19), Barett's oesophagus (1/16) or large gastric polyps requiring polypectomy (2/19). The 97 patients without verifiable pathology at endoscopy were

double-blindly randomized to either continuous omeprazole 20 mg daily or tapering from same dose to 10 mg every other day. After 3 weeks all patients discontinued the treatment. The study found that 27% of the total study group were off PPI at the 1-year follow-up. In the tapering group 31% were off PPIs compared to 22% in the non-tapering group (a non-significant difference). A diagnosis of GORD and the serum gastrin level at baseline were independent predictors of reinstitution of PPI.

The Danish study by Zwisler (11) included 171 patients who had been prescribed antisecretory medication [histamine-2-receptor antagonists (H2RAs) or PPIs] for >2 out of the 6 previous months. The patients had no history of oesophagitis, high risk of ulcer (previous peptic and current use of ulcerogenic drugs) or serious comorbidities. All participants were included by their GP, tested for *H. pylori* and given eradication therapy if tested positive.

The patients discontinued their usual treatment and were double-blindly randomized to either placebo or esomeprazole 40 mg. The patients were 39–79 years old, over half of them had nicotine use but no excessive use of alcohol. On average they had had symptoms for 4 years and ~50% of them had had an endoscopy performed. Approximately 60% were taking non-steroidal anti-inflammatory drugs (NSAIDs). There was no significant difference in demographic or clinical measures between the two groups.

The primary outcome of the study was the need to discontinue trial medication and reinstitute usual antisecretory treatment. During the 1-year follow-up, 71% discontinued the placebo and 19% discontinued esomeprazole treatment. This means that 29% of those randomized to placebo treatment were still off PPIs and having sufficient symptom control after 1-year follow-up, while 81% of those randomized to esomeprazole remained on esomeprazole.

In another Danish study conducted by Reimer *et al.* (12), the prescription registers of 22 GPs were searched and 654 patients were identified who had been prescribed at least 120 tablets of PPI in the previous 12 months without a verified indication. Only patients without serious comorbidities and willing to undergo endoscopy were included (78 patients). These patients were significantly younger than those excluded or not willing to undergo endoscopy (mean age 56 vs. 61 years, $P < 0.01$) but comparable in terms of sex, prescribed number of tablets, prevalence of previous gastroscopy, *H. pylori* testing and co-prescription of NSAIDs.

All were asked to discontinue their PPI after inclusion; and if the patients had symptom recurrence requiring resumption of therapy, an endoscopy was performed. If the endoscopy was normal, the patients were double-blindly randomized to either esomeprazole 40 mg or placebo. The primary outcome measure was the difference in proportion with treatment success after a week of therapy between the groups.

A total of 14% (11/78) discontinued their usual PPI successfully, 68% (53/78) had recurrence of symptoms requiring resumption of therapy within 6 months. Of those, 81% (43/53) had symptom relapse within the first 4 weeks. No significant predictors of outcome among patient characteristics (age, gender, duration of PPI treatment, reflux symptoms, co-prescription of NSAIDs, previous attempts to withdraw PPI or previous endoscopy) were identified. All 53 patients with symptom relapse had an endoscopy performed and those without verifiable pathology [58% (31/53)] were double-blindly randomized to either esomeprazole 40 mg once daily or placebo for a week. After 7 days, 12/15 (80%) in the actively treated group experienced relief compared to 2/16 (13%) in the placebo group ($P < 0.001$).

The American study by Inadomi *et al.* (13) aimed to prospectively evaluate the feasibility of step-down therapy of PPIs in a cohort of patients treated for symptoms of uncomplicated GORD. The primary outcome was successful step-down, defined as continued relief of GORD symptoms without use of PPIs for 1 year.

A total of 376 outpatients from general medicine clinics at a regional medical centre were identified as having been prescribed PPIs for >8 weeks. A total of 155/376 (41%) attended the clinic for evaluation of eligibility of step-down management. Only patients with symptoms of GORD and complete alleviation by continuous use of PPIs could were included. A total of 71 patients met inclusion criteria. The mean age was 62 years (29–85) and they been taking PPIs for 21 months (4–45). Their mean BMI was 27.8 (18–42.9), 28% were smokers and 33% had weekly consumption of alcohol.

The patients stepped-down by halving their dose of PPI (those already on lowest dose discontinued right away) and after 2 weeks they discontinued PPI if no symptom relapse occurred.

In case of relapse the patients were instructed to contact the clinic for administration of H2RAs and/or prokinetics. If this proved insufficient the original PPI dose was reinstituted.

At the 1-year follow-up, 58% (41/71) were off PPIs, but 73% (30/41) required H2RAs and/or prokinetics. In spite of the majority still needing treatment, the authors estimated a significant annual net saving. As secondary outcome measures, the authors found that the patients' quality of life and disease severity did not differ significantly between baseline and at the 6- and 12-month follow-up.

The quality of the three randomized controlled trials (RCTs) by Zwisler *et al.*, Krol *et al.* and Björnsson *et al.* was assessed using the Jadad scale, which focuses on the parameters randomization procedure, blinding and follow up. The results of the quality assessment are shown in Table 2.

Table 2. Quality assessment of the RCTs included ad modum Jadad

	Krol *et al.* (9)	Björnsson *et al.* (10)	Zwisler (11)
Randomization	1	1	2
Blinding	0	2	2
Account of all patients	1	1	1
Total Jadad scale score	2	4	5

Discussion

This review demonstrates that several interventions can be made in order to decrease use of PPIs. Discontinuations without deteriorating symptom control were reported across all six studies ranging from 14% to 64%, with discontinuation persisting for more than a year. Two of the studies included dose reduction as an endpoint and showed that 30–50% of the patients were able to lower the dose. A major strength of this review is the comprehensive search strategy, which was conducted guided by the PRISMA 2009 Checklist and AMSTAR Checklist for systematic reviews. Despite an extensive search strategy, a limitation of this review is the possibility of incomplete retrieval of identified research. The fact that one of the studies was unpublished and identifiable only through ClinicalTrials.gov exemplifies a risk of publication bias. However, the degree of publication bias cannot be further assessed by, e.g. funnel plot because there were <10 studies included. Another limitation of the review is the design quality of the studies that were analysed. The studies giving the highest discontinuation rates were non-randomized, non-controlled single centre studies. The lack of a control group makes it difficult to evaluate the contribution of the intervention to the frequency of discontinuation/dosage reduction. Three of the studies were RCTs. The quality of the RCTs was assessed according to the Jadad scale on the parameters randomization procedure, blinding and follow up (Table 2). Only one of the three RCTs (Zwisler *et al.*) meets all criteria for a well-performed RCT.

One of the studies (Murie *et al.*) had a potential conflict of interest with one of the authors being employed by the manufacturers of an alginate used to manage breakthrough symptoms when discontinuing PPIs. In the rest of the studies included we did not find any potential conflicts of interest.

The underlying pathology or diagnoses for initiating therapy differ between studies. In two trials, the indication was unknown while others included GORD and NUD patients. However, in some studies it was unclear whether the GORD diagnosis was established based on the patient's symptoms, oesophageal manometry and pH monitoring or endoscopy. Differences in discontinuation rates must be expected according to symptom severity and whether the cause of the symptoms was truly acid-related or not.

Five of the studies focused only on discontinuation of PPIs while one of the studies included long-term users of both PPIs and H2RAs. All studies were able to identify a noteworthy number of patients treated with antisecretory medication without a verifiable indication. One of the studies found that almost one-fifth of patients were treated with a double standard dose of PPI without a clear indication, disregarding guidelines recommending a high-dose treatment only for severe oesophagitis (Los Angeles Grade C or D) or the rare Zollinger-Ellison's syndrome (14).

It is striking that there was no consensus on how discontinuation should be attempted and therefore no similarity in the discontinuation regimens. Tapering appeared to be more successful than abrupt discontinuation. This might reflect the clinical relevance of hypergastrinemia and rebound acid hypersecretion following discontinuation of only a few weeks of antisecretory treatment. This is supported by the fact that serum gastrin level is an independent predictor of need for reinstitution of PPI therapy (10). In addition, despite endoscopy revealed no pathology, the majority of patients with symptom reoccurrence after drug discontinuation were relieved by reinstitution of PPI therapy when compared to placebo (12).

Future randomized controlled clinical trials comparing different strategies for discontinuation are needed. None of the studies included stated theoretical considerations for their choice of discontinuation regimen. When designing a discontinuation strategy for evaluation it would be relevant to take the time for normalization of serum gastrin into account in order to minimize the risk of acid-rebound leading to resumption of therapy.

Due to lack of homogeneity in design, setting and strategy for discontinuation in the retrieved studies, it is not possible to make a clear conclusion about which strategy is the most effective for withdrawing antisecretory treatment. However, this review indicates that a substantial decrease in use of PPIs is achievable, when supported by advice on dose tapering, the possibility of rebound symptoms within the first weeks and giving an alginate or antacid to manage potential breakthrough symptoms. The fact that all discontinuation regimens studied have proven effective despite substantial differences in their design indicates that at least some of the effect might be a result of intervening rather than a result of the intervention itself.

Key points

- A substantial number of patients treated with proton pump inhibitors (PPIs) without a clear indication can step down or completely off PPIs without deteriorating symptom control.
- Tapering seems to be a more effective strategy than abrupt discontinuation, possibly due to hypergastrinemia and rebound acid hypersecretion after long-term use of PPIs.
- Future randomized clinical trials comparing different strategies for discontinuation and taking the time period for normalization of serum gastrin into account are needed in order to make a clear conclusion on the most effective tapering time period.

Declaration

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Conflict of interest: none.

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