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Systematic review: the efficacy of intermittent and on-demand therapy with histamine H_2-receptor antagonists or proton pump inhibitors for gastro-oesophageal reflux disease patients

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SUMMARY

Aim: To perform a systematic review on the efficacy of intermittent and on-demand therapy with either histamine H_2-receptor antagonists or proton pump inhibitors for patients with erosive oesophagitis or symptomatic heartburn.

Method: We conducted randomized-controlled trials of non-continuous therapy in gastro-oesophageal reflux disease patients.

Results: Fourteen studies met inclusion criteria. Because of variation in outcome measures statistical pooling of results was not possible. Results were analysed qualitatively. Four studies evaluated intermittent therapy of treatment 3 days a week with omeprazole 20 mg or daily with ranitidine which were not efficacious compared to a daily proton pump inhibitor. Famotidine 10 and 20 mg, ranitidine 75 mg and cimetidine 200 mg were efficacious in five on-demand studies for relief of symptomatic heartburn episodes. In three of four studies, evaluating only non-erosive (endoscopy-negative) gastro-oesophageal reflux disease patients, esomeprazole 20 and 40 mg and omeprazole 10 and 20 mg a day were efficacious using willingness to continue as an endpoint. Lansoprazole 30 mg and omeprazole 20 mg maintained symptom control in 60–70% of healed oesophagitis patients.

Conclusions: Intermittent proton pump inhibitor or H_2-receptor antagonist therapy is not effective in maintaining control in oesophagitis patients. H_2-receptor antagonists are effective for relief of heartburn episodes. On-demand proton pump inhibitor therapy may work in a proportion of non-erosive gastro-oesophageal reflux disease patients.

INTRODUCTION

Population-based studies report that weekly upper gastrointestinal (GI) symptoms of moderate severity occur in 8–20% of the general population,[1, 2] but there are only limited data available on the prevalence of use of acid suppressive therapy. Studies estimate that 1–4% of the population takes prescription acid suppressive treatment with either histamine H_2-receptor antagonists (H_2RAs) or proton pump inhibitors (PPIs), most often for gastro-oesophageal reflux disease (GERD).[3–5] Some reports show much higher rates, especially in the elderly.[6]

Most patients with GERD have dominant symptoms of heartburn and/or acid regurgitation. GERD can result in oesophageal mucosal injury, usually erosive oesophagitis (EE). It is estimated that 50–70% of GERD patients never develop oesophagitis, and such patients are referred as having non-erosive GERD (NERD).[7, 8] More than 80% of GERD patients need acid suppressive medications to control their symptoms. Relapse of

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symptoms occur in up to 70–80% of both oesophagitis and NERD patients after they finish an initial course of therapy. Consequently, maintenance treatment is often required for ongoing symptom control.[9, 10] Resulting medication costs for GERD patients are high. There is evidence that treatment of GERD significantly improves quality of life (QoL).[11]

The goals of treatment for GERD are threefold: control of symptoms, healing of oesophagitis (if present) and the prevention of complications (stricture, Barrett's oesophagus and oesophageal adenocarcinoma). The proportion of GERD patients that do not require a daily dose of acid suppression to maintain symptom control is estimated to be 20–40%. Patients may voluntarily switch from daily maintenance dosing to a self-directed regimen where medication is taken intermittently to relieve symptoms.[12–14] There are several forms of non-continuous therapy: (i) intermittent; (ii) on-demand; and (iii) 'threshold' therapy. For intermittent therapy, patients take medication for a certain period (for example, 7 or 28 days) after relapse of symptoms. With on-demand therapy patients take medication only when symptoms occur; each time they wait for a relapse of symptoms to occur. For 'threshold' therapy, patients gradually increase the interval between medications (for example, to every second or third day) as long as symptoms do *not* recur. To date threshold therapy has not been studied.

Recently, several intermittent and on-demand studies in GERD patients have been reported. The objective of this study was to perform a systematic review on the efficacy of intermittent and on-demand therapy with acid suppressive medication for GERD patients. The specific objectives were to determine whether intermittent or on-demand therapy: (i) achieved control of GERD symptoms; (ii) was efficacious in preventing relapse of oesophagitis in patients with erosive disease; and (iii) prevented long-term sequelae of GERD, especially stricture, development of Barrett's oesophagus or oesophageal adenocarcinoma.

METHODS

Identification of studies

The Medline database (from January 1966 to December 2004) and the Cochrane Controlled Trials Register were searched. The search terms used were: (on-demand OR intermittent) AND (gastroesophageal reflux OR oesophagitis OR heartburn OR prevention OR stricture OR Barrett's esophagus OR esophageal adenocarcinoma). Limits employed in this search were English, Human and double-blind randomized-controlled trial (RCT). Review articles were also sought using the same search terms to help identify additional original studies. A careful review of references was conducted of all retrieved articles. Only studies published in full were included. The inclusion criteria were: studies of GERD patients with or without EE, random allocation to treatment groups, double-blind study, use of PPIs and/or H_2RAs and assessment of the efficacy of intermittent and/or on-demand therapy.

A data extraction form was developed to standardize the methodological and quantitative information that was extracted from each study (available from authors on request). This consisted of: in/exclusion criteria of patients in the study, diagnosis (EE/non-erosive reflux disease), study design, drug regimens used, duration of treatment, sample size, number of drop outs, patient setting (GI clinics or primary care), main outcome measures used to assess efficacy and study conclusion. Each study was reviewed by three authors and differences were resolved through discussion.

RESULTS

Results of medline and cochrane search

The Medline search (final date December 2004) resulted in 33 citations, of which 12 met inclusion criteria. The reason for excluding 13 of the other 21 Medline citations was that GERD patients were not investigated.[15–27] Reasons for excluding the remaining eight studies were that: the efficacy of intermittent and/or on-demand therapy was not assessed ($n = 4$),[28–31] the study was single-blind or open-label ($n = 2$),[32, 33] lack of randomization of on-demand phase ($n = 1$)[34] and the article was a synopsis of a published study ($n = 1$).[35] The Cochrane search found four additional citations, none of which met inclusion criteria because they did not investigate GERD patients.[36–39] Three additional articles were found in reference sections of other studies (one did not meet the inclusion criteria due to lack of randomization to a comparison group).[40] This left a total of 14 eligible studies. Of the 14 included studies: four articles assessed intermittent therapy for GERD,[41–44] five articles examined on-demand therapy with H_2RAs[45–49] and five articles investigated on-demand therapy with PPIs.[50–54] Eight[41, 42, 46, 50–54]

studies were conducted in GI clinics (i.e. dealing with patients referred to GI clinics), two[48, 49] in primary care, two[43, 44] in both GI clinics and primary care and two[45, 47] were out-patient trials (in one[53] study recruitment sites were not stated).

Only minor disagreements between reviewers occurred during the data extraction phase which were resolved through discussion. Because of the marked variation in outcome measures (see Table 1) it was not possible to perform a formal meta-analysis, that is a statistical pooling of results. Instead, the results were analysed in a qualitative fashion.

There were no studies that looked at the effectiveness of on-demand or intermittent therapy in preventing long-term sequelae, especially formation of stricture, Barrett's oesophagus or oesophageal adenocarcinoma.

INTERMITTENT THERAPY

Patients on intermittent therapy take medication upon symptom recurrence for a fixed duration (for example, 7 or 28 consecutive days). Four RCTs[41–44] investigated the efficacy of intermittent therapy. One of these studies (Wiklund *et al.*[44]) assessed QoL measures as part of the investigation by Bardhan *et al.*[43] Table 2 summarizes main features of these studies.

In the study by Dent *et al.*,[41] 159 patients with EE of grade ≥2 at baseline and who achieved healing (EE grade 0 or 1) with 4-week (or 8 weeks, if required) treatment of omeprazole 20 mg daily were enrolled in the follow-up phase consisting of three treatment groups: omeprazole 20 mg daily (OME20-daily), omeprazole 20 mg on Fridays, Saturdays and Sundays (OME20-int) and ranitidine 150 mg twice daily (RAN). Outcome measures were relapse of EE and symptoms over the 12-month duration of the study.

Symptoms (heartburn, regurgitation, dysphagia and nausea) were assessed at 1, 2, 3, 6, 9 and 12 months and were graded as: none, mild, moderate or severe. Endoscopy took place at 6 and 12 months, or if patients presented with moderate to severe symptoms for 3 days in any given week (symptom relapse). Endoscopic relapse was defined as endoscopically verified EE of grade 2 or more and such patients discontinued the study. The proportion of patients without a relapse of EE and with symptom relapse over the 12-month treatment period can be seen in Table 2. It is clear that the majority of patients with EE grade 2–4 require daily PPI treatment and cannot be controlled on intermittent PPI or continuous H_2RA treatment as both the recurrence of oesophagitis and symptom relapse occur at a rate that is too high to be acceptable.

Table 1. Outcome measures used in intermittent and on-demand studies

	Outcome measure(s) used
Intermittent	
Dent *et al.*[41]	Proportion of patients without relapse of EE and experiencing moderate to severe symptoms (symptom relapse)[1]
Sontag *et al.*[42]	Proportion of patients without relapse of EE and without symptom relapse[1]
Bardhan *et al.*[43]	Total time off active treatment measured in days, time to failure of intermittent treatment[1]
Wiklund *et al.*[44]	QoL measured by PGWB and GSRS[1]
On-demand with H_2RAs	
Simon *et al.*[45]	Proportion of heartburn episodes relieved; relief assessed hourly by patient[1]
Galmiche *et al.*[46]	Proportion of patients experiencing relief of ≥75% of heartburn episodes[1]
Faaij *et al.*[47]	Time to onset of relief for a single heartburn episode[1]
Johannessen *et al.*[48]	Time until symptom relief[1]
Elm *et al.*[49]	Time until symptom relief and number of successfully relieved episodes with symptoms[1]
On-demand with PPIs	
Lind *et al.*[50]	Discontinuation because of unwillingness to continue[1] Mean number of study drug and antacid tablets used per day, consecutive days taking drug and QoL measured by PGWB and GSRS[2]
Talley *et al.*[51]	Discontinuation because of unwillingness to continue[1] Mean number of study drug and antacid tablets used per day and consecutive days taking drug[2]
Talley *et al.*[52]	Discontinuation because of unwillingness to continue[1] Mean number of study drug and antacid tablets used per day and consecutive days taking drug[2]
Bytzer *et al.*[53]	Discontinuation because of inadequate heartburn control[1] Use of rescue antacids and severity of heartburn[2]
Johnsson *et al.*[54]	Number of study drug consumed per day[1]

PGWB, Psychological General Well-Being; GSRS, Gastrointestinal Symptom Rating Scale; EE, erosive oesophagitis; QoL, quality of life.
[1] Primary outcome measure.
[2] Secondary outcome measure(s).

Table 2. Main features of studies that assess intermittent therapy

	Inclusion	Interventions	Outcomes	Results		
Dent *et al.*[41] $n = 159$	Healed grade 2–4 EE from initial 4–8-week treatment with OME 20 mg daily	12 months of: OME 20-daily, $n = 53$ OME 20-int, $n = 55$ or RAN, $n = 51$	% remaining healed of EE Proportion with symptom (heartburn, regurgitation, dysphagia or nausea) relapse	Treatment group	% remaining healed of EE after 12 months (95% CI)	% experiencing moderate to severe symptoms (relapse)
				OME20-daily	47/53, 89% (80–98%)*	8/53, 15%
				OME20-int	18/55, 32% (19–46%)	37/55, 67%
				RAN	13/51, 25% (13–38%)	29/51, 57%
				*Significant result ($P < 0.001$) vs. OME20-int and RAN No statistical test results are given for symptom data		
Sontag *et al.*[42] $n = 406$	Healed grade 2–4 EE from initial 4–8-week treatment with OME 40 mg daily	6 months of OME 20-daily, $n = 138$ OME 20-int, $n = 137$ or PLC, $n = 131$	% remaining healed of EE (endoscopy at 4, 12 and 24 weeks) Proportion of patients without symptom relapse Symptoms assessed using a 5-point and 4-point Likert scale for severity	Treatment group	Relapse rate: % free from oesophagitis after 6 months	Symptom recurrence: % with no change/slight worsening of symptoms
				OME20-daily	97/138, 70%**	100/132, 74%**
				OME20-int	47/137, 34%*	50/135, 37%*
				PLC	14/131, 11%	13/127, 10%
				**Significant result ($P < 0.001$) vs. OME20-int and PLC *Significant result ($P < 0.001$) vs. PLC		
Bardhan *et al.*[43] $n = 677$	Moderate to severe heartburn for >2 days in the 2 weeks prior to study or LA grade A–C EE	12 months of RAN 150 mg b.d., $n = 229$ OME 20 mg od, $n = 221$ OR OME 10 mg od, $n = 227$ upon symptom relapse, taken for 14 or 28 days	% of patients completing intermittent therapy and switching to daily maintenance therapy Total time off active treatment Time to failure of intermittent treatment Number of symptom relapses	47% ($n = 318$) completed study on intermittent therapy 24% ($n = 161$) switched from intermittent to daily maintenance therapy 29% ($n = 197$) discontinued study mainly due to loss to follow-up ($n = 58$), an adverse event ($n = 51$) or because of unwillingness to continue ($n = 21$) Median no. of days off treatment for all patients = 142 out of 365 (39%) 50% of patients did not need therapy for at least 6 months Symptom relapses; 40% had none, 30% had one, 15% had two and 8% had three Proportions from each treatment group completing intermittent therapy (46–48%) and switching to daily maintenance therapy (22–27%) were similar		

Sontag *et al.*[42] investigated in 406 patients whether healing of EE could be maintained and recurrence of symptoms prevented, with intermittent dosing of omeprazole over a 6-month period. Patients with grade 2–4 EE first received 4–8 weeks of omeprazole 40 mg daily until healing of EE (from grade 2–4 to grade 0 or 1) was confirmed endoscopically. If patients achieved EE grade 0 or 1 and experienced less than three consecutive days of heartburn in the final week they were randomly assigned to one of three groups: omeprazole 20 mg daily (OME20-daily), omeprazole 20 mg for three consecutive days per week and placebo (PLC) on the remaining four days (OME20-int) or PLC. Success of treatment was defined as the absence of relapse of EE and/or recurrence of symptoms. Symptoms were assessed using a 5-point scale evaluating heartburn severity and a 4-point scale evaluating frequency of symptoms. Results are outlined in Table 2.

In patients with healed grade 2–4 EE, OME20-daily was superior, when compared with OME20-int and PLC, in preventing relapse of EE and recurrence of symptoms. PLC was inferior to OME20-int, however, overall endoscopic and symptomatic relapse rates were also high (66 and 63%, respectively) in the OME20-int group.

Bardhan *et al.*[43] assessed the efficacy of intermittent therapy over 12 months. A total of 684 patients were enrolled: 33% ($n = 223$) had a normal endoscopy, 28% ($n = 190$) had Los Angeles classification (LA) grade A, 32% ($n = 217$) had LA grade B and 8% ($n = 54$) had LA grade C EE. For 677 of the included patients the results of therapy are reported.

Patients were randomized into one of three groups: ranitidine 150 mg twice daily (RAN), omeprazole 10 mg once daily (OME10) or omeprazole 20 mg once daily (OME20), all given for 14 consecutive days. Patients were entered in the 12-month follow-up period if, after the initial 2 weeks of treatment, they had no or mild symptoms during the previous seven days. Patients who were still symptomatic after 14 days had the dose doubled (if in the RAN or OME10 group) or continued with the initial dose (if in the OME20 group) for an additional 2 weeks.

If symptomatic relapse (defined as moderate to severe symptoms for ≥2 days in each of the previous 2 weeks) occurred during the follow-up period, patients received a course of intermittent therapy consisting of 14 consecutive days (or 28, if needed to further ameliorate symptoms) with the same treatment that initially controlled symptoms. All subsequent relapses were treated the same way. Treatment failure was defined as patients having ongoing symptoms despite initial 4-week continuous treatment or if the level of symptom control was unacceptable to the patient (unwillingness to continue). Study outcomes and results can be seen in Table 2. Of all 677 patients, approximately 47% ($n = 318$), 9% ($n = 61$), 8% ($n = 54$) and 36% ($n = 244$) had 0–3, 3–6, 6–9 and 9–12 months of therapy, respectively, during the study.

The conclusion of this study was that for half (47%) of patients with LA grade A–C EE, intermittent treatment with omeprazole is an effective treatment option to control symptoms. However, the way the results of the study were reported makes the assessment of individual treatments difficult. Results were not presented according to endoscopy status. Although it is reported that endoscopic grade of EE at entry is not a prognostic factor for remaining in the study, it is unclear what the proportion is of patients with NERD and EE (of different grades) that remained on intermittent therapy.

Quality of life during intermittent treatment in patients with GERD was investigated[44] as part of the previous study (not in Table 2; features of study are the same as in the Bardhan *et al.*[43] investigation) using the validated Psychological General Well-Being (PGWB) index and the Gastrointestinal Symptom Rating Scale (GSRS). Of the 677 patients from the previous study, 584 completed QoL forms to make up the study population.

The OME10 (mean difference = 4.2) and OME20 (mean difference = 3.2) groups both had PGWB scores that were significantly higher compared with RAN ($P = 0.005$ and $P = 0.031$, respectively). Although statistically significant the differences are small and unlikely to be clinically important. Differences in PGWB scores between OME10 and OME20 were not significant. Compared with RAN, the OME10 regimen resulted in significant improvement in total GSRS score (mean difference = 0.18, $P = 0.006$). There were no differences in GSRS scores between OME20 and RAN or OME10. Relapse of symptoms led to significant decreases in QoL measures which were restored with further (intermittent) treatment. Upon first symptom relapse, intermittent treatment resulted in improvement of GSRS (from 2.3 to 1.5) and PGWB (from 96.9 to 105.9) scores. This magnitude of improvement in QoL scores is likely to be clinically meaningful.

Thus, it was concluded that QoL in NERD and LA grade A–C EE can be improved with intermittent

therapy. Interestingly no differences in QoL were seen between patients with and without EE either before or after treatment. However, it is unclear from this study whether the changes in QoL in part depend on the severity of EE as the results for grade of oesophagitis were not reported separately.

ON-DEMAND THERAPY WITH H_2RAs

Characteristics and results of the following five RCTs[45–49] are outlined in Table 3. Patient settings were described above. The study by Elm *et al.*[49] was randomized but not double-blinded. The two studies by Johannessen *et al.*[48] and Elm *et al.*[49] used a crossover design. The three remaining studies by Simon *et al.*,[45] Galmiche *et al.*[46] and Faaij *et al.*[47] used a parallel group design. Three of these five studies were multicentre.[45, 46, 49]

The efficacy of on-demand therapy with famotidine 20 mg (FAM20), 10 mg (FAM10), 5 mg (FAM5), antacid (ANT) and PLC was investigated[45] in 565 patients suffering from episodic heartburn. Patients did not undergo endoscopy. This was a trial to determine whether famotidine would be effective as an over the

Table 3. Main features of (five) studies that assess on-demand therapy with H_2RAs

	Inclusion	Interventions	Outcomes	Results
Simon et al.[45] $n = 565$	Out-patients with heartburn, not originally seeking care for heartburn	FAM 5 mg FAM 10 mg FAM 20 mg ANT 11 mEq PLC all given on-demand ≤ 2 times daily	Proportion of symptoms relieved	FAM20 & FAM10 (not FAM5) vs. PLC had a higher proportion of episodes relieved (FAM20–69%, FAM10–70%, PLC-41%, $P < 0.001$ for both groups vs. PLC). ANT also provided more relief than PLC ($P < 0.05$)
Galmiche *et al.*[46] $n = 1289$	Episodic heartburn for ≥3 months with ≥4 episodes the week before the study	RAN 75 mg, $n = 504$ CIM 200 mg, $n = 515$ PLC, $n = 270$ all given on-demand ≤ 3 times daily Antacids, if needed after 2 h after third dose	Proportion of patients experiencing relief of ≥75% of heartburn episodes	RAN, 41% = 207/504** CIM, 38% = 196/515* PLC, 28% = 76/270 No difference between RAN and CIM
Faaij *et al.*[47] $n = 94$	Moderate heartburn for ≥ twice per month	ANT 10 mL, $n = 49$ RAN 75 mg tablet, $n = 45$ 3-h duration	Time to onset of relief for a single heartburn episode VAS & PRR measured symptom relief	ANT reduced heartburn quicker than RAN (19 min vs. 70 min, $P = 0.04$) For time to total pain relief, ANT (135 min) worked faster than RAN (165 min) but difference was not significant ($P = 0.43$)
Johannessen et al.[48] $n = 829$	GERD ≥1 year Treatment required >4/7 days/week in month prior to study	FAM wafer 20 mg RAN 150 mg tablet Single crossover (doses at least 24 h apart)	Time until symptom relief, measured via 7-point Likert scale	No difference found (P = not sig.) in efficacy scores after 3 h between RAN (4.66) and FAM (4.56)
Elm *et al.*[49] $n = 102$	GERD for ≥3 months 3–7 treated day heartburn episodes in the 2 weeks prior to study	$n = 53$, RAN 150 mg tablets first $n = 49$, RAN 150 mg effervescent tablets first Rescue antacids allowed, if sufficient relief did not occur within 60 min of dosing	Time until symptom relief Number of relieved episodic symptoms	Mean time to relief; RAN-eff (27 min) less than RAN-std (36 min), $P < 0.001$ More episodes of symptoms adequately treated with RAN-eff than RAN-std (82% vs. 73%, $P = 0.02$)

* $P < 0.01$ vs. PLC.
** $P < 0.001$ vs. PLC.

counter drug. Patients were instructed over a 4-week period to self-administer the drug as needed, up to twice daily, to treat heartburn episodes. Rescue antacids were provided to patients if the test drug did not sufficiently relieve symptoms. The time allowed before rescue antacids could be used, after the study drug was taken, was not specified. Relief was defined as the absence of symptoms after study drug was taken, without rescue antacid use.

Results are listed in Table 3. This study shows that self-treatment with FAM20, FAM10 or ANT (but not FAM5), is effective in controlling heartburn episodes.

The purpose of the study by Galmiche *et al.*[46] was to compare the efficacy of ranitidine 75 mg (RAN) to cimetidine 200 mg (CIM) or PLC given on-demand during a 15-day period in 1289 patients with episodic heartburn and no history of moderate to severe EE (≥ grade 2, Savary-Miller classification). This study was carried out to determine whether ranitidine 75 mg would be effective as an over the counter drug. Medication could be taken up to three times daily, with at least a 2-h interval. Relief was defined as lasting five or more hours within two hours of drug ingestion and was recorded on a diary card.

Significantly more patients in the RAN (41% = 207/504, $P < 0.001$) and CIM (38% = 196/515, $P < 0.01$) groups, compared to PLC (28% = 76/270), experienced relief of at least 75% of heartburn episodes during the study (primary outcome as seen in Table 3). The differences between RAN and CIM were not significant. This study demonstrates that low-dose RAN or CIM given on-demand provides significantly more relief of GERD symptoms when compared to PLC.

The study by Faaij *et al.*[47] compared the onset of relief for a single episode of heartburn between a 10 mL Maalox suspension (ANT) and low-dose ranitidine (75 mg, RAN), taken on-demand, in 94 patients with self-perceived heartburn of moderate severity.

Data was collected using an electronic diary which was used by patients when they experienced a heartburn episode that warranted treatment. A Visual Analogue Scale (VAS) was used to measure the intensity of symptoms (0–100 mm). Response to trial medication was measured at 60, 90, 120 and 180 min using a five-item pyrosis (heartburn) relief rating (PRR) scale. The PRR ranges from strong symptom deterioration (0) to strong symptom improvement (4). The authors did not stipulate what amount of difference in PRR between treatment groups was clinically meaningful. The time to complete heartburn relief was defined as the first time a participant had complete absence of heartburn for 30 min.

There were no significant differences between the two groups with regards to VAS scores over the 180-min evaluation period. The ANT group had a PRR score (3.43) 60 min after dosing that was significantly better than the score of the RAN group (3.04). However, PRR scores for RAN improved over the 60–180-min time period, whereas ANT relief scores did not. After 3 h, PRR scores of the two on-demand treatment groups were similar (ANT = 3.45 vs. RAN = 3.73).

In people with symptomatic heartburn ANT (Maalox®, 10 mL suspension) provided faster symptom relief than RAN (75 mg). However, in both groups, relief of heartburn was incomplete in over half the participants.

The study by Johannessen *et al.*[48] compared the immediate effects of single dose treatment of a famotidine 20 mg wafer (FAM) to a ranitidine 150 mg tablet (RAN) in 829 GERD patients.

Patients were randomly assigned to receive either FAM-RAN or RAN-FAM for on-demand treatment of heartburn. An interval of at least 24 h between the FAM-RAN or RAN-FAM dose was part of the single crossover study design. Each test dose was to be taken on an as needed basis to relieve reflux symptoms. Response was measured by the patients at 15, 30, 45, 60, 120 and 180 min after dosing using a seven-point Likert scale that ranged from worse (1) to unchanged (2) to total relief of symptoms (7). There was no difference (4.56 and 4.66) in symptom response between the FAM and RAN groups.

A similar crossover study by Elm *et al.*[49] investigated a single dose of a standard ranitidine 150 mg tablet (RAN-std) to a ranitidine effervescent 150 mg tablet (RAN-eff) in 102 GERD patients. As shown in Table 3, compared with RAN-std, RAN-eff relieved more episodic symptoms in less amount of time, although it is uncertain how clinically meaningful the differences are.

ON-DEMAND THERAPY WITH PPIs

Five randomized clinical trials[50–54] assessed the efficacy of PPIs given on-demand over a 6 month period. In all five studies initial short-term (4–8 week) daily treatment was administered to achieve complete resolution of heartburn. All of these studies employed the use of

the Medical Event Monitoring System which records the date and time of each opening and closure of the medication container. Four studies[50–53] only enrolled endoscopy-negative (NERD) patients and three[50–52] used the same primary efficacy variable: time to discontinuation of on-demand therapy due to unwillingness to continue. Study characteristics and results are outlined in Table 4. Patients were instructed to take one study drug capsule daily when experiencing heartburn, and for as many days needed, until symptom resolution occurred. Rescue antacid medication was provided and to be taken only if needed. In contrast, the study by Johnsson *et al.*[54] included patients with EE, lacked a PLC comparison group, did not allow antacid use, permitted two trial capsules per day and primarily assessed the average number of capsules consumed per day to control symptoms.

The study by Lind *et al.*[50] randomized 424 patients into one of three groups: omeprazole 20 mg (OME20), omeprazole 10 mg (OME10) or PLC. Other outcome variables included dosing frequency and PGWB and GSRS scores to assess QoL.

After 6 months of on-demand therapy, the percentage of patients willing to continue was 83% for OME20, 70% for OME10 and 56% for PLC; $P \leq 0.01$ between all three groups. Of the 30% (129 of 424) of study patients unwilling to continue, 91% (118 of 129) left the study due to inadequate relief of heartburn. In patients unwilling to continue, PGWB scores fell to the same low levels (OME20-95, OME10-96, PLC-101) seen prior to the start of initial continuous treatment. In contrast, the PGWB scores of patients who were willing to continue remained higher (OME20-104, OME10-107, PLC-104) than a normal healthy population (103).[55] There were no significant differences between the three treatment groups according to the GSRS.

With regards to dosing patterns, as seen in Table 4, OME20 (taken on-demand) results in approximately a 50% reduction (0.43 capsules used per day) in medication utilization. The use of antacids as rescue medication was highest in PLC.

The authors concluded that omeprazole given on-demand is an effective treatment strategy for the majority of NERD patients, although an average of 0.77–0.91 doses of antacids per day are taken in addition.

In the study by Talley *et al.*[51] 342 patients were assigned to one of two treatment arms: esomeprazole 20 mg (ESO20) or PLC. Of 111 of 342 (32% of study patients) unwilling to continue the study, all but one case was due to insufficient control of heartburn. After 6 months of on-demand therapy, the percentage of patients willing to continue was significantly higher for ESO20 (145 of 170, 85%) when compared with PLC (83 of 172, 48%), $P < 0.0001$.

A significantly greater proportion of PLC than ESO20 patients took trial medication for periods of 4–6 and 7–13 consecutive days (see Table 4). This difference further supports the greater percentage of PLC than ESO20 patients unwilling to continue the study due to inadequate symptom relief. Furthermore, 50% (85 of 170) taking ESO20 had one or less days of heartburn in the previous 7 days compared with only 27% (46 of 172) of the PLC group, $P < 0.0001$.

The study's investigators concluded that ESO20 given on-demand is an effective treatment strategy for long-term symptom control in NERD patients with an average requirement of 0.34 treatment doses per day.

The other study by Talley *et al.*[52] compared the efficacy of esomeprazole 40 mg (ESO40) and esomeprazole 20 mg (ESO20) to PLC in 721 NERD patients. Of 116 of 721 (16% of study patients) unwilling to continue the study, 92 of 116 (79%) cases were because of insufficient control of heartburn. ESO40 and ESO20, compared with PLC, had significantly higher proportions of patients willing to continue. No significant difference was found between ESO40 and ESO20 ($P = 0.15$).

ESO40, ESO20 and PLC dosing patterns, seen in Table 4, suggest that trial medication was taken once every 3 days. The authors concluded that ESO40 and ESO20 given on-demand are effective for maintaining heartburn control in NERD patients.

In the study by Bytzer *et al.*,[53] initially 523 patients with NERD who had at least 3 days of moderate to severe heartburn in the 7 days prior to enrollment, were treated for 4 weeks with open label rabeprazole 10 mg once a day. Of these, 432 (83%) achieved complete symptom relief and were randomized to on-demand treatment with rabeprazole 10 mg once a day (RAB10) or identical looking PLC. The primary outcome measure was discontinuation in the study because of inadequate control of heartburn. This occurred in 20% (28 of 139) of PLC treated compared to 6% (16 of 279) in the RAB10 group. The use of rescue antacids was twice as high in the PLC group compared with the RAB10 group. PLC treated patients also had significantly worse severity of heartburn compared with rabeprazole treated patients. The authors concluded

Table 4. Studies that assess on-demand therapy with PPIs – willing to continue rates and dosing patterns

Study (6-month trials)	Treatment groups (*n*)	Willing to continue (%)†	Mean number of study drug/day	Mean number of antacid tablets/day	≥1 consecutive period for	% of patients using drug for given consecutive time period
Lind *et al.*[50]	OME20 (139)	115 (83)**	0.43	0.77	≥7 days	54% of all study patients (229/424)
n = 424, NERD	OME10 (142)	99 (70)*	0.41	0.91	≥14 days	26% of all study patients (110/424)
	PLC (143)	80 (56)	0.47	1.15	≥28 days	13% of all study patients (55/424)
Talley *et al.*[51]	ESO20 (170)	145 (85)*	0.34*	0.39*	4–6 days	ESO20, 22% (37/170) – $P = 0.04$ vs. PLC
n = 342, NERD	PLC (172)	83 (48)	0.41	1.06		PLC, 32% (55/172)
					7–13 days	ESO20, 11% (19/170) – $P = 0.03$ vs. PLC
						PLC, 21% (36/172)
Talley *et al.*[52]	ESO40 (293)	272 (93)*	0.29	0.48*	4–6 days	ESO40, 20% (59/293) – *P*-values not stated
n = 721, NERD	ESO20 (282)	257 (91)*	0.33	0.44*		ESO20, 24% (68/282)
	PLC (146)	88 (60)	0.40	1.07		PLC, 27% (39/146)
					7–13 days	ESO40, 11% (32/293) – *P*-values not stated
						ESO20, 10% (28/282)
						PLC, 23% (34/146)
Bytzer *et al.*[53]	RAB10 (279)	Discontinued because of	NA	Mean weekly	NA	NA
n = 535, NERD 432	PLC (139)	lack of heartburn control		antacid use*		
randomized		RAB10–16 (6)		RAB10–2.0		
		PLC 28 – (28)		PLC – 3.9		
		Sufficient heartburn control				
		RAB10–241 (86)				
		PLC – 94 (68)				
Johnsson *et al.*[54]	LAN30 (154)	–	0.73	—	Up to two tablets	
n = 300, grade ≤ 3 EE	OME20 (146)	–	0.72	—	per day permitted	

** Significant *P*-value vs. PLC and other PPI regimen.
* Significant *P*-value vs. PLC.
† Intention-to-treat analysis.
OME, omeprazole; ESO, esomeprazole; RAB, rabeprazole; LAN, lansoprazole; PLC, placebo; NA, not available.

that rabeprazole 10 mg is effective for on-demand treatment in NERD patients.

In the final study reviewed here by Johnsson *et al.*,[54] 300 patients (with EE grade ≤ 3) were randomized to either lansoprazole 30 mg (LAN30) or omeprazole 20 mg (OME20). GERD symptoms were assessed at three clinical visits during the 6-month trial. There were no differences in the severity or types of GERD symptoms between the treatment groups at all three visits. The majority of patients were free from heartburn (70%, 210 of 300) and acid regurgitation (60%, 180 of 300) while taking on average 0.72–0.73 tablets/day, meaning that the decrease in drug use compared to once daily dosing is small.

The findings of this study suggest that both LAN30 and OME20, taken on-demand, are equally effective in maintaining symptom control in patients with EE who were healed with 4 weeks of twice daily PPI dosing. In this study, patients took more medication (see Table 4) than in the NERD studies.[50–52]

DISCUSSION

The few data available in the literature suggest that 1–4% of the population takes chronic acid suppressive therapy.[3–5] Although it is said non-continuous therapy is often practiced, little data are available in the literature regarding this. We recently conducted a review of 100 000 recipients of the Nova Scotia Pharmacare Program.[6] Patients are eligible for this program if they are aged 65 and older. Approximately one-third of patients took H_2RAs or PPIs continuously, 11% 7–9 months a year, 17% 4–6 months a year and 39% 1–3 months a year.[6] This data suggests that intermittent or on-demand therapy is commonly used by patients.

Our systematic review had three objectives, to determine whether on-demand or intermittent therapy is effective: (i) to prevent relapse of oesophagitis in patients with EE; (ii) in patients with erosive or NERD to prevent relapse of reflux symptoms; and (iii) to prevent long-term sequelae of GERD such as stricture, Barrett's oesophagus, or oesophageal adenocarcinoma.

With regard to the prevention of long-term sequelae currently there are no published studies which have addressed this issue. It seems unlikely that RCTs will ever be conducted for this purpose although relevant data possibly could be obtained from prospective cohort studies. There is evidence from database studies that over the last 10 years the proportion of patients undergoing endoscopy who require dilatation for a peptic stricture has diminished. This decrease coincided with more widespread use of PPIs.[56]

Extensive searches were done to identify studies of intermittent or on-demand therapy for GERD patients. Despite the very large number of treatment trials using either H_2RAs or PPIs, it was a surprise that only 14 studies evaluated intermittent or on-demand therapy. Interestingly, only two studies recruited patients exclusively from primary care practices which is likely the setting where patients with less severe GERD are seen and where non-continuous therapy would be expected to be most effective. It should be noted that the studies evaluating H_2RAs were mainly done to obtain over the counter status for these medications for treatment of symptomatic heartburn episodes.

The question whether intermittent or on-demand therapy is efficacious in preventing relapse of oesophagitis in patients whose baseline endoscopy did document EE was addressed in four studies which evaluated intermittent and one study which tested on-demand therapy. There is unequivocal evidence that in EE patients, daily maintenance therapy is effective in preventing relapse of oesophagitis. However, a proportion of patients may not require continuous therapy.[12–14] Non-continuous therapy is attractive, as it may lower drug use and result in cost savings. Intermittent therapy is defined as a course of therapy of fixed duration (for example, 2–4 weeks) upon symptomatic relapse. Patients being treated on-demand, only use medication when symptoms occur and for as long as is needed until symptoms are relieved. Intermittent therapy has been shown in the pre-*Helicobacter pylori* duodenal ulcer (DU) literature to be an effective and safe way to treat symptoms.[57–60] On-demand treated DU patients consumed less (ranitidine 150 mg) tablets (57 vs. 195, $P < 0.001$) over a 7-month period leading to significant cost savings compared to the group treated with continuous maintenance therapy.[61]

Our systematic review shows that intermittent therapy has low efficacy in patients with grade A–C/1–3 EE (Table 2). No studies have evaluated intermittent therapy in NERD patients. In the one on-demand study of EE patients, lansoprazole and omeprazole were equally effective although it should be stressed that on average patients took 0.7 doses of medications per day, which in essence makes it very comparable to continuous maintenance therapy. One reason why PPIs may

not be suitable for on-demand therapy in EE is their relatively slow onset of action. From the patient's perspective it may take too long before symptoms are controlled as with non-continuous treatment one would want to have fast relief of symptoms. More on-demand PPI therapy studies need to be performed in EE, especially LA grade A and B to determine whether this treatment strategy is effective.

Most on-demand PPI therapy data[50–54] come from studies of NERD patients which make up 50–70% of all GERD cases.[8] Our review shows that on-demand PPI therapy can be effective in treating 83–93% of NERD patients, reducing use of drugs and rescue antacids. Antacid use varied from 0.39 to 1.15 tablets per day in these studies which may contribute to the control of symptoms. Only one study investigated on-demand PPI therapy in EE patients and estimated that 60–70% were free from symptoms, with an average of 0.72–0.73 tablets being used per day. For the latter study the difference compared to once daily dosing therefore is small and likely of little clinical significance. Other narrative reviews, which were less explicit in systematically analyzing outcome measures, also concluded that on-demand therapy can work in NERD but not oesophagitis patients.[62–65]

In addition, two single blind studies have been published evaluating on-demand PPI therapy in NERD and in primary care uninvestigated GERD patients. In the study by Meineche-Schmidt *et al.*,[32] it was shown that on-demand therapy did lead to cost savings and was acceptable to patients. In the study by Tsai *et al.*,[33] it was found that 80–93% of NERD patients treated on-demand with either lansoprazole 15 mg or esomeprazole 20 mg were willing to continue with on-demand therapy.

Outcome measures in on-demand studies

Typically, newly diagnosed GERD patients are given an initial 4–8-week daily treatment to determine whether effective control of symptoms can be achieved. Intermittent or on-demand therapy is only given if patients do indeed have complete or near complete response to therapy. Starting initially with daily treatment also allows the patient to judge what kind of symptom control is possible and what happens with their symptoms if a switch to non-continuous therapy is made.

There is a lack of consensus in the literature on what outcome measures to use in non-continuous (intermittent and on-demand) treatment to document efficacy. In this review much variation was found in the choice of outcome measures making comparisons difficult. The marked variation in outcome measures made it impossible to statistically pool results for a meta-analysis. Relapse of heartburn as an outcome measure has high face validity especially if both its frequency and severity is assessed. For willingness to continue it is less clear whether patients are satisfied with on-demand therapy just because they remain in a study. Patients may be satisfied with on-demand therapy even though they are still required to take medication daily or almost daily for prolonged periods. The number of days that medications are used and the frequency of need for rescue antacids are other clinically important outcome measures.

Other options include severity of individual symptoms, especially heartburn and acid regurgitation, and the number of symptom free days. There is some data in the literature which does suggest that if patients have more than twice a week mild severity of heartburn or at least once a week moderate severity of heartburn that health-related QoL diminishes.[66] This type of outcome measure could be evaluated further and is potentially useful.

Studies assessing on-demand PPI therapy for NERD and EE

The most frequently used outcome measures in NERD studies[50–52] were the proportion of patients willing to continue, the need for use of study drug for consecutive day periods (see Table 1) and necessity of using rescue antacids (see Table 4). These studies do make clear that on-demand therapy with a PPI is efficacious in a substantial proportion of NERD patients. For the esomeprazole studies the mean number of study drug taken varied from 0.29 to 0.43 a day and antacids 0.44 to 0.91. Rabeprazole 10 mg compared with PLC was also efficacious in one study using the rate of discontinuation because of inadequate control of heartburn as the main outcome measure. For infrequent brief symptomatic episodes of heartburn, medications with a rapid onset are required and antacids are useful for this purpose.

The on-demand H_2RA studies were mainly performed to obtain approval for over the counter status for famotidine and ranitidine. Three studies[47–49] assessed the onset of treatment effect (symptom relief) and preference of H_2RA formulation. Results showed that famotidine 10 and 20 mg and ranitidine 75 mg were better than PLC and that the onset is rapid (within an hour of dosing), although not as fast as antacids. As

study duration was only 2–4 weeks,[45, 46, 49] it is unclear whether on-demand therapy with H_2RAs is effective when used long-term.

Threshold therapy

In addition to intermittent and on-demand therapy, conceptually there is a third form of non-continuous therapy, which we refer to as 'threshold' therapy. For 'threshold' therapy, the patient titrates the medication down to a frequency that still maintains adequate control of symptoms. This is different from on-demand therapy where each time the patient waits for recurrence of symptoms. The latter certainly is an option if heartburn episodes are very infrequent but if such episodes occur regularly 'threshold' therapy may be attractive. To date no threshold therapy trials have been conducted but we believe this therapy merits studying.

CONCLUSION

Given the high prevalence of GERD it is surprising how few studies have investigated non-continuous (intermittent and on-demand) therapy. To date there are no studies which have determined whether intermittent or on-demand therapy can prevent the long-term sequelae of GERD, that is stricture, Barrett's oesophagus and oesophageal adenocarcinoma. There is evidence that in patients with Los Angeles grade B–D oesophagitis, intermittent or on-demand therapy is inadequate in preventing relapse of both oesophagitis and reflux symptoms and such patients require long-term daily maintenance therapy. Whether this is also true for Los Angeles grade A oesophagitis is not known. For patients with non-erosive reflux disease (NERD) on-demand therapy does work in a substantial proportion of patients and could be attempted. In practice many patients seen in primary care are uninvestigated and they will not have undergone endoscopy. For these patients control of reflux symptoms should be the main goal of therapy and an empiric trial of acid suppression makes clinical sense. Finally, over the counter H_2RAs and antacids are efficacious in relief of symptomatic heartburn episodes although antacids work faster but for a shorter duration. Further studies of on-demand therapy, intermittent and threshold therapy are needed as are studies on the development and evaluation of outcome measures for non-continuous therapy.

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