American Journal of Gastroenterology
© 2007 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2006.00998.x

CLINICAL REVIEWS

On-Demand Therapy for Gastroesophageal Reflux Disease

David C. Metz, M.D.,[1] John M. Inadomi, M.D.,[2] Colin W. Howden, M.D., F.A.C.G.,[3] Sander J. Veldhuyzen van Zanten, M.D., Ph.D.,[4] and Peter Bytzer, M.D., Ph.D.[5]

[1]*University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania;* [2]*Division of Gastroenterology, San Francisco General Hospital, and Department of Medicine, University of California San Francisco, San Francisco, California;* [3]*Northwestern University, Feinberg School of Medicine, Chicago, Illinois;* [4]*Queen Elizabeth II Health Sciences Centre, Department of Medicine, Halifax, Nova Scotia, Canada; and* [5]*University of Copenhagen, Copenhagen, Denmark*

The following pages summarize the proceedings of a symposium held in May 2006 on the emerging role of on-demand therapy for gastroesophageal reflux disease (GERD). Medical therapy for GERD has undergone significant change in recent years with the advent of effective, but expensive, antisecretory agents. On-demand (patient-driven) therapy is attractive to payers and patients, because it appears to be both cost-effective and convenient. Many individuals appear to accept occasional symptomatic breakthrough in exchange for personal control of their disease. On-demand therapy should be distinguished from intermittent therapy, which is either patient- or physician-driven, but which requires intermittent episodes of continuous therapy followed by discontinuation until symptoms recur. Proton pump inhibitors appear to be effective on-demand agents despite theoretical pharmacodynamic limitations for this class of drug. The available data support the use of on-demand therapy for GERD in uninvestigated reflux disease, nonerosive reflux disease, and possibly mild esophagitis as well. On-demand therapy should not be considered for patients with severe esophagitis.

(Am J Gastroenterol 2007;102:642–653)

INTRODUCTION

Gastroesophageal reflux disease (GERD) therapy has undergone significant change in recent years following the advent of effective, but expensive, antisecretory medications. The following pages summarize the proceedings of a symposium held in May 2006 on the emerging role of on-demand therapy for GERD.

ECONOMIC IMPERATIVES

It is estimated that 60 million people in the United States have heartburn at least once per month (1). Symptoms of GERD result in 4.6 million office encounters annually if one counts only the primary reason for the visit, or 9.1 million visits annually if one includes visits in which a GERD diagnosis was listed as one of the top three diagnoses for the encounter (2). The direct costs for GERD management were estimated at $9.3 billion in 1998 (2). The breakdown of direct costs was as follows: drugs ($5.9 billion), hospital inpatient admissions ($2.5 billion), physician office visits ($603 million), hospital outpatient visits ($213 million), and hospital emergency visits ($78 million). Indirect costs due to lost days of work add an additional $480 million per year to the total costs of GERD care (2, 3). Thus, national GERD management costs approach $10 billion annually. In contrast, costs incurred due to other gastrointestinal diseases are substantially less. Colorectal cancer ($5.3 billion), peptic ulcer disease ($3.4 billion), chronic liver disease including hepatitis C infection ($2.5 billion), inflammatory bowel disease ($1.2 billion), and Barrett's esophagus ($390 million) all fall short of the expenditures related to GERD care (2).

It is evident that any effort to substantially reduce the financial burden of GERD must be aimed at reducing the costs of medical therapy. It is in this context that the topic of on-demand therapy for GERD generates increasing interest. In contrast to traditional continuous proton pump inhibitor (PPI) therapy for GERD, on-demand dosing refers to the administration of medication in response to symptoms, discontinuing drug after symptoms abate. This is in contrast to intermittent dosing whereby medication is also administered in response to symptoms but is continued for a specified duration regardless of when symptoms respond. In addition to the health economic aspect of on-demand therapy, patient preference has also been identified as a driving force behind this form of therapy. Patients already use PPIs on-demand. Twenty to 29% of patients prescribed PPIs decreased the frequency of administration without advice from their provider, with adherence to PPIs being associated with symptom severity and patient preference for "as needed" therapy (4, 5). Moreover, among patients prescribed continuous PPIs, 79% did not refill their prescriptions in a manner sufficient to remain fully adherent to their dosing schedule (6). It is apparent from these data that patients accept and may prefer on-demand dosing to continuous PPI therapy.

A systematic review of the literature was conducted to evaluate studies of the economic impact of noncontinuous, including on-demand and intermittent, PPI administration for GERD. The search was conducted in Medline and Embase and consisted of the key words: (gastroesophageal reflux disease OR GERD OR reflux esophagitis) AND (cost-effectiveness OR economic). Retrieved articles were included if they examined on-demand or intermittent PPI administration. Studies were excluded if they did not contain original analyses, or were published in languages other than English.

Eight studies fulfilled inclusion and exclusion criteria (Table 1) (7–14). The majority of examined populations were comprised of either patients with GERD symptoms empirically treated with PPIs, or patients with GERD symptoms who were endoscopically confirmed to be free of erosive disease. Additionally, most studies assumed that symptoms had to be initially relieved by the PPI to be considered for noncontinuous therapy. Of the included studies, three examined intermittent strategies of PPI administration defined as short (2–8 wk) courses of daily PPI administration for recurrence of GERD symptoms, but did not evaluate on-demand strategies (7–9). The remaining five studies included true on-demand dosing, defined as administration of a PPI in response to recurrence of acute symptoms of GERD. Of the on-demand studies, one compared on-demand with intermittent and continuous PPI administration (10), one compared on-demand with intermittent dosing (11), one compared on-demand with continuous PPI or continuous histamine H2 receptor antagonist (H_2RA) therapy (12), and two were limited to comparison of on-demand administration with various PPI brands and/or formulations (13, 14). While the majority of studies used mathematical modeling with computer simulation to predict health-care outcomes, two studies were based on randomized clinical trials in which economic data were compiled in conjunction with other clinical outcomes (11, 12).

Of the five studies that included primary (initial) continuous PPI administration as a comparator, three concluded that this strategy achieved the greatest efficacy in terms of prevention of symptomatic relapse (7, 8, 12). Surprisingly, the remaining two studies predicted better outcomes using noncontinuous PPI administration. One of these studies used quality-adjusted life-years as the primary effectiveness outcome, thus the advantage of noncontinuous PPI administration (in this case intermittent therapy) may have been due to the decreased need for diagnostic tests or because patients prefer to control their medication dosage (9). The other study compared on-demand esomeprazole with continuous omeprazole, thus the advantage of on-demand therapy was based on the heightened efficacy of esomeprazole in preventing symptomatic relapses of GERD symptoms compared with omeprazole (10). The latter was also one of the two included studies that compared on-demand with intermittent strategies of PPI administration and revealed an advantage for on-demand esomeprazole compared with intermittent omeprazole, likely for the same reason. The second study comparing on-demand with intermittent dosing of esomeprazole failed to illustrate a difference in efficacy; however, because on-demand dosing required lower expenditures, it became the dominant strategy, defined as a strategy that is as or more effective, yet less expensive, than comparator strategies (11).

Two recent studies compared on-demand administration of specific PPIs, using continuous administration for persistent symptoms in patients with GERD symptoms or nonerosive reflux disease (13, 14). It is difficult to support significant superiority in terms of symptom resolution with on-demand dosing among standard PPI preparations; thus, this exercise is best viewed as a cost-minimization analysis in which the preferred strategy is based on the lowest health-care expenditures. In this case, over-the-counter (OTC) PPIs, not included in either analysis, would be expected to emerge as a preferred strategy if based on U.S. cost data. None of the retrieved studies examined the potential advantages of more rapidly acting PPI preparations such as uncoated omeprazole administered with bicarbonate; nevertheless, it is premature to identify a single PPI that may be optimal for on-demand administration.

In none of the eight included studies was on-demand or intermittent PPI administration demonstrated to be dominated (less effective and more expensive) by alternative strategies. Moreover, on-demand or intermittent PPI administration consistently demonstrated an incremental cost-effectiveness ratio that enabled them to represent viable strategies to manage patients with symptoms of GERD. When compared with step-up or step-down strategies, in which less expensive forms of medication are used either prior to starting PPIs or after response to PPIs is demonstrated, intermittent and on-demand strategies were either dominant or associated with favorable cost-effectiveness ratios (8, 9).

Thus, compared with continuous PPI administration and step-up or step-down strategies, on-demand PPI administration represents a reasonable "bang for the buck" to treat GERD symptoms in appropriate patients. In addition to decreased resource utilization, on-demand strategies are attractive, because some patients achieve greater satisfaction due to self-regulation of medication administration. Based on evidence supporting the efficacy of symptom control with noncontinuous PPI administration and the fact that patients already use PPIs in an on-demand fashion, it is reasonable for health-care providers to encourage this strategy in an effort to reduce the economic burden of GERD management.

PHARMACOLOGIC IMPERATIVES

Antacids, H_2RAs, and PPIs may all be taken on-demand for GERD management, although the PPIs are not FDA-approved for such use. Antacids, H_2RAs, an H_2RA-antacid combination product, and omeprazole can be purchased OTC. The most desirable attributes of a medicine for on-demand use in GERD are rapid onset of action, prompt symptom control, simplicity of dosing, safety, and the lack of a requirement for physician supervision. Antacids are the most rapidly acting; they do not require systemic absorption and work

Table 1. Systematic Review of the Economic Impact of Noncontinuous PPI Therapy

Reference	Population	Design/Time Frame	Strategies	Cost Direct health-care costs ($)	Clinical Outcome Symptom recurrences	Comparison ICER ($ per symptom recurrence prevented)
Am J Med 1997	EE healed by PPI	Markov model	Intermittent PPI: continuous after 2 relapses	$865	1.33	–
		1 yr	Intermittent PPI: continuous after 1 relapse	$908	0.75	$74
			Continuous PPI (Intermittent PPI = 8 wk courses)	$1,376	0.18	$467
				Direct health-care costs ($CAN)	Weeks with GERD	ICER ($CAN/GERD week averted)
Pharmacoecon 1999	EE	Decision tree	Continuous H_2RA	$657	10.41	–
		1 yr	Intermittent PPI (8 wk courses)	$678	7.78	$8
			Step down: PPI to H_2RA	$748	6.17	$44
			Step down: standard PPI to low-dose PPI	$955	5.54	Dominated
			Continuous PPI	$1,093	4.82	$256
				Direct health-care costs ($US)	dQALYs [mild/severe]	ICER ($US/QALY gained) [mild/severe]
Am J Gastroenterol 2000	GERD symptoms	Decision tree	Lifestyle modifications	$0	24.38/23.66	–
		Age 40 yr to death	Intermittent PPI (8 wk courses)	$26,167	25.07/24.91	$37,923/$20,934
			Step up: H_2RA to PPI	$27,846	24.55/24.37	Dominated
			H_2RA to EGD, PPI for EE	$29,965	24.66/24.42	Dominated
			Step down: PPI to H_2RA	$37,641	24.66/24.43	Dominated
			Continuous PPI	$41,112	24.76/24.65	Dominated

(*Continued.*)

Table 1. Continued.

Reference	Population	Design/Time Frame	Strategies	Cost Direct health-care costs (£)	Clinical Outcome Symptom relapses	Comparison ICER (£ per symptom relapses prevented)
Pharmacoecon 2002	NERD	Markov model	On-demand esomeprazole 20 mg	£63	0.10	–
		6 months	Intermittent omeprazole 20 mg	£75	0.57	Dominated
			Continuous omeprazole 20 mg	£96	0.47	Dominated
				Total direct ± indirect costs	Symptom relapses	ICER (€/symptom relapse prevented)
Aliment Pharm Ther 2004	GERD symptoms relieved by PPI	Randomized clinical trial	On-demand esomeprazole 20 mg	€ 211	0.13	–
		6 months	Intermittent esomeprazole 40 mg x 4 wk	€ 300	2.08	Dominated
			Intermittent esomeprazole 40 mg x 2 wk (Intermittent = PCP prescribed)	€ 344	2.82	Dominated
				Total direct ± indirect costs	% with relapse	ICER (€/symptom relapse prevented)
Int J Clin Prac 2005	GERD symptoms relieved by PPI	Randomized clinical trial	On-demand esomeprazole 20 mg*	€ 222	10.9%	–
		6 months	Continuous ranitidine 300 mg bid[c]	€ 287	34.4%	Dominated
			Continuous esomeprazole 20 mg*	€ 296	7.0%	€ 1,897
			*(Failure: intermittent esomeprazole 40 mg x 4 wk)			
			[c](Failure: intermittent ranitidine 300 mg bid x 4 wk)			

(*Continued.*)

Table 1. Continued.

Reference	Population	Design/Time Frame	Strategies	Cost Direct health-care costs (£US)	Clinical Outcome QALYs	Comparison ICER (£ QALY gained)
Curr Med Res Opin 2005	GERD symptoms	Markov model	omeprazole generic	£285	0.981	£0
		1 yr cost/QALY	Rabeprazole	£294	0.982	£8,308
			Pantoprazole	£329	0.981	Dominated
			Lansoprazole solutabs	£336	0.980	Dominated
			Esomeprazole	£358	0.980	Dominated
			Lansoprazole capsules	£359	0.980	Dominated
			Omeprazole branded	£399	0.981	Dominated
			(each PPI modeled with combined continuous, on-demand, step-down strategies)			
				Direct health-care costs	Utilities	Cost minimization
Pharmacoecon 2005	NERD relieved by PPI	Mathematical model	On-demand rabeprazole 10 mg	€ 123	0.89	Lowest direct health-care costs
		1 yr	On-demand pantoprazole 20 mg	€ 176	0.90	–
			On-demand esomeprazole 20 mg	€ 190	0.89	–
			On-demand lansoprazole 15 mg	€ 195	0.91	–
			On-demand omeprazole 20 mg	€ 201	0.90	–
			On-demand omeprazole 10 mg	€ 210	0.91	–

GERD = gastroesophageal reflux disease; EE = erosive esophagitis; NERD = nonerosive reflux disease; PPI = proton pump inhibitor; H_2RA = histamine 2 receptor antagonist; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; EGD = esophagogastroduodenoscopy.
Direct health-care costs include medication expenditures, outpatient visits, hospitalizations.
Total direct costs include direct health-care costs plus direct non-health-care costs, which include transportation costs incurred by patients.
Indirect costs include resource loss due to work absence or lost leisure time.

intraluminally through chemical neutralization of acid. H_2RAs take longer to produce their effect because of the requirement for absorption. PPIs are the most effective agents overall for GERD management, but also have the longest delay between ingestion and onset of action.

H_2RAs are competitive antagonists of histamine at parietal cell H_2 receptors. They are widely used on-demand for relatively mild, infrequent heartburn. Although they are recommended for both treatment and prevention of food-related heartburn, eating substantially reduces their antisecretory effect (15, 16). Because their inhibitory effect can be overcome through vagal or gastrin stimulation, they are not particularly effective at preventing food-stimulated gastric acid secretion during the day.

Repeated daily use of H_2RAs is associated with diminution of their pharmacodynamic effect, which may be seen as early as the fifth day (17–22). This is generally attributed to the development of pharmacological tolerance, perhaps due to H_2 receptor upregulation. The phenomenon of tolerance has been demonstrated with all the H_2RAs. There is also rebound acid hypersecretion following discontinuation of H_2RA treatment. Response to both H_2-receptor agonists and antagonists is enhanced following discontinuation (23) and levels of acid secretion are elevated above pretreatment values for up to 6 wk (24). This phenomenon has been associated with the development of new gastrointestinal symptoms in previously asymptomatic volunteer subjects (25). However, neither tolerance nor rebound hypersecretion should be serious considerations for the on-demand use of H_2RAs in GERD.

PPIs are acid-labile pro-drugs that are required to be absorbed systemically and are initially widely distributed throughout the body. Preferential uptake of circulating PPIs by parietal cells is promoted by food ingestion. Once taken up by parietal cells, PPIs must be extruded through the luminal aspect of the parietal cell membrane, undergo protonation and then conversion to their active sulphenamide form, and subsequently bind covalently to membrane-bound molecules of H^+/K^+-ATPase (26).

Available agents differ with respect to their binding to, and uncoupling from, H^+/K^+-ATPase and to the specific cysteine residues to which they bind. However, these have not been associated with any substantive differences in clinical outcomes (26). There are minor pharmacokinetic differences among currently available PPIs, although all have a relatively short elimination half-life of between 1 and 2 h. Absolute bioavailability within the first few doses differs among the agents. Omeprazole and esomeprazole have relatively low bioavailability on initial dosing, which increases progressively during the first few days and typically reaches a plateau after 5 days. While this might imply that these drugs would be impractical for on-demand use in GERD, evidence from randomized, placebo-controlled trials attests to their effectiveness (27). Other PPIs—including lansoprazole, pantoprazole, and rabeprazole—have also been shown to be superior to placebo for the on-demand treatment of GERD. There have been few head-to-head comparisons among the PPI class, although one trial reported at Digestive Disease Week in 2006 showed no significant difference between lansoprazole and rabeprazole when taken on-demand (28).

Although pharmacokinetic and pharmacodynamic criteria imply that PPIs might appear less appropriate for on-demand use in GERD than other more rapidly acting agents, randomized controlled trials against placebo consistently demonstrate that many patients are satisfied with them (27) and PPIs are effective when used on-demand. Because most trials have focused on GERD patients without erosive esophagitis, on-demand PPI use should primarily be considered for patients with endoscopy-negative reflux disease. The adequacy and safety of on-demand PPI treatment for patients with erosive esophagitis remain to be demonstrated in studies and its use in higher grades of esophagitis should be discouraged.

An uncoated, immediate-release formulation of omeprazole in sodium bicarbonate is available as a powder and as a capsule. Administration of omeprazole in this manner is associated with more rapid systemic absorption and a faster onset of antisecretory effect compared with standard capsules of enteric-coated omeprazole granules (29, 30). When taken at bedtime, this product produces more effective control of nocturnal intragastric acidity than some traditional delayed-release PPIs taken before the evening meal or at bedtime (31, 32). The on-demand use of this product has not been studied and therefore it is unknown whether this agent is superior to standard PPI on-demand therapy for GERD.

The potassium-competitive acid blockers (P-CABs) are currently still in development, and it is currently unclear if they will be used in an on-demand manner for the treatment of GERD or even introduced into clinical practice at all. After oral administration, they are rapidly absorbed and become highly concentrated in the secretory canaliculi of parietal cells, where they are rapidly protonated. They inhibit H^+/K^+-ATPase through reversible, ionic, noncovalent binding at the site for ingress of potassium ions. They produce more rapid inhibition of acid secretion than the PPIs but also have a shorter duration of action (33). In a comparative trial in erosive esophagitis, single daily doses of 25 mg to 75 mg of AZD0865 were no more effective than esomeprazole 40 mg for healing or for relieving symptoms (34). In endoscopy-negative reflux disease, AZD0865 25–75 mg once daily was no more effective than esomeprazole 20 mg once daily in relieving symptoms (35). A dose-dependent increase in liver transaminase levels was seen with AZD0865 and with an earlier prototypical P-CAB SCH28080 (33). The development of AZD0865 has now been discontinued.

In summary, antacids and H_2RAs will continue to be widely used on-demand by patients with episodic heartburn. PPIs are effective in patients with endoscopy-negative GERD when taken on-demand. Although there are minor pharmacokinetic differences within the class, there is no evidence that these predict superiority of any particular agent for on-demand use. Drugs that may be used on-demand in the

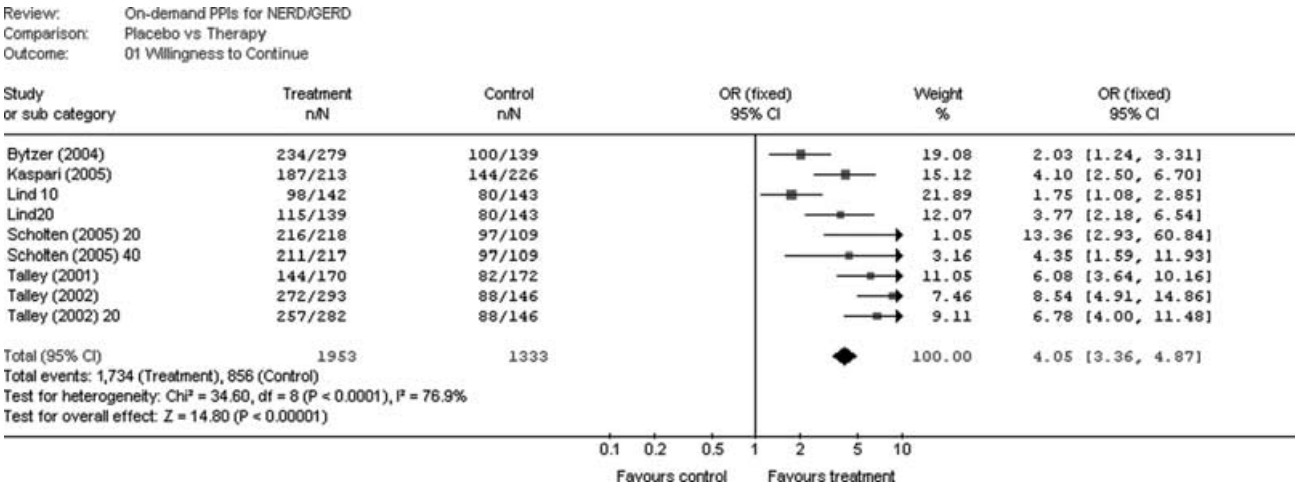

Figure 1. Forrest plot for the outcome measure willingness to continue or discontinuation due to lack of heartburn control compared with placebo.

future include immediate-release, buffered PPIs without enteric coating, and—possibly—P-CABs.

AVAILABLE DATA

The goals of GERD therapy are resolution of symptoms, to the point that symptoms are no longer bothersome for the patient (36), normalization of the patient's health-related quality of life, and prevention of long-term consequences such as Barrett's esophagus and strictures in patients with endoscopic abnormalities. There are three options available for "noncontinuous" long-term therapy: "true" on-demand therapy, intermittent therapy, and "threshold" therapy (37). For on-demand therapy, the patient waits for symptoms to return, then takes medication for as long as symptoms are present. Once symptoms have subsided, treatment is stopped (38). For intermittent therapy, the patient takes short courses of therapy for a predefined number of days and then stops (38). Conceptually, threshold therapy is the most attractive, but it has never been studied in GERD trials. In this case, the patient titrates down the medication to the lowest frequency that controls symptoms, *e.g.*, once every second, third, or fourth day. There is evidence that many users of PPIs and H_2RAs do take their medication noncontinuously (39).

A wide variety of outcome measures have been used in on-demand and intermittent therapy studies, and these include: number of heartburn-free days, willingness to continue or discontinuation because of insufficient heartburn control, mean number of tablets of study drug therapy taken, mean number of rescue antacids taken, quality of life, costs, and relapse of esophagitis, if erosive esophagitis patients were studied (37). There is increasing evidence that severity and frequency of heartburn is a reliable measure of how bothersome symptoms are and how it may affect quality of life (40). In patients who had mild GERD symptoms more than twice a week or any heartburn of at least moderate severity, quality of life was diminished.

A systematic review evaluating intermittent and on-demand therapy for GERD was published recently (37) and it has been updated for this article. For a study to be eligible in the meta-analysis, patients had to have either a diagnosis of erosive esophagitis or nonerosive reflux disease, and studies had to be double blind and randomized.

INTERMITTENT THERAPY

Four studies were identified. One of these described quality of life results of one of the other studies leaving three studies for analysis. Two studies evaluated patients with erosive esophagitis, and one study included both erosive esophagitis and patients suffering from minor to severe heartburn. In all of these studies, intermittent therapy was given as weekend therapy with omeprazole 20 mg a day given on Fridays, Saturdays, and Sundays. This is different from intermittent therapy given in "old" duodenal ulcer therapies, where treatment was usually given for several weeks after symptoms recurred (37). The GERD intermittent studies made clear that weekend therapy is not efficacious in patients with erosive esophagitis, as up to 66% of patients had a relapse of erosive esophagitis and up to 63% a relapse of reflux symptoms. There are insufficient data to determine whether intermittent therapy is effective in nonerosive reflux disease.

ON-DEMAND THERAPY

Five studies evaluated on-demand therapy of the H_2RAs, ranitidine 75 mg, and famotidine up to 20 mg a day (37). Most of these studies were carried out to obtain OTC approval status for these drugs. All studies showed that the H_2RAs were superior to placebo for self-directed treatment of episodic heartburn. Antacids were superior to placebo and worked faster than the H_2RAs, but for a shorter duration. Both famotidine 10 mg and 20 mg were more effective than placebo as

was ranitidine 75 mg. Effervescent ranitidine was faster and more potent than ranitidine tablets, demonstrating that formulation of H_2RAs is important for the speed of heartburn relief.

The systematic review of on-demand therapy studies with PPIs identified five studies, four of which were conducted in patients with nonerosive reflux disease and one in erosive esophagitis (37). A systematic review conducted by Moayyedi also included single-blind and open-label studies (41). All studies start with 4–8 wk of continuous PPI therapy and patients are only randomized to the on-demand part of the studies if symptom control is achieved. As mentioned above, outcome measures varied and included willingness to continue or discontinuation because of insufficient heartburn control, mean number of study drugs taken, and mean number of rescue antacids taken. Since our published review in 2005, two more double-blind, randomized, controlled trials were identified (42, 43).

Figure 1 shows the Forrest plot for the outcome measure of willingness to continue or discontinuation due to lack of heartburn control as compared with placebo. The odds ratio of 4.05 is statistically significant but so is the test for heterogeneity, indicating that there is inherent variation in studies. However, inspection of the Forrest plot also makes it clear that the variation only deals with the magnitude of difference not whether or not active treatment is superior to placebo. Part of this variation may be due to variation in placebo response, which varied from 50% to 80%. This suggests that there were inherent differences among enrolled patients in the different studies.

In a different meta-analysis, Moayyedi also showed that on-demand therapy is not as efficacious as continuous PPI treatment (41). However, this conclusion was based on the inclusion of open-label and single-blind studies.

Many studies did not report standard deviations around the average number of PPI tablets taken each day by patients, making it impossible to pool the data for this outcome measure. In the Moayyedi meta-analysis (41), the calculated average daily number of PPI tablets taken was 0.39 (95% CI 0.30–0.58).

In addition to the above-mentioned on-demand studies in erosive and nonerosive reflux disease patients, there is one randomized controlled trial comparing on-demand therapy with lansoprazole 30 mg a day to omeprazole 20 mg a day in 300 patients who had erosive esophagitis grade 1–3 (44). In this study, there was no difference between the two treatments, but the mean number of days that study drug was taken was high, 0.72–0.73. This suggests that in most patients with erosive esophagitis, it is not possible to change to on-demand therapy.

It is important to keep in mind while assessing studies of on-demand therapy, that for ethical reasons, it is necessary to allow use of rescue antacids. The need for acid suppression with either an H_2RA or a PPI may be decreased by use of antacids, as they themselves can improve heartburn symptoms. In the meta-analysis, the average number of rescue antacids taken varied from 0.39 to 1.06 tablets per day (37). As virtually all studies of on-demand therapy have been done with nonerosive reflux disease patients, it is unclear whether this strategy works in patients with erosive esophagitis, in particular grade A. The evidence does seem to suggest that on-demand therapy is not efficacious in patients with esophagitis grade B or higher.

RECOMMENDATIONS

Many patients with symptoms of GERD who are prescribed continuous treatment only take their medication when symptoms become troublesome, apparently content to experience relapse of symptoms. A symptom-driven management approach (on-demand therapy) is therefore an option for these patients and it has proven beneficial in patients with relatively infrequent symptom relapses. On-demand dosing allows patients to take their medication only if symptoms are present. Patients should be instructed to start taking medication when they first experience heartburn and to stop treatment when they have been free of symptoms for at least 24 h. Only one dose of PPI should be permitted each day.

There are several rationales, apart from the economic, in support of on-demand treatment strategies. For many reflux patients, symptom attacks are relatively short and the duration of attacks can be further shortened by a start of treatment without delay. The strategy stimulates the patient's sense of responsibility and fits well into many patients' intuitive self-regulation of reflux therapy and their desire to remain in personal control. Prescription studies have shown that patients on long-term PPI therapy take their treatment on less than 50% of the days (5, 6). Even patients with erosive esophagitis take medication on less than 60% of days if instructed in an on-demand dosing regimen (44). Symptoms are an important reminder to take medication and many patients with reflux disease are symptom-free for long periods. In primary care patients with upper gastrointestinal symptoms, there is a 40% probability that 2 consecutive days have different symptom levels, only 10% of patients show stable symptoms, and patients are completely symptom-free for 20% of the time (45).

Symptom control should be the key aim of therapy (46). However, not all patients expect complete absence of symptoms in the long term. It has been the experience from clinical trials that many reflux patients are willing to continue a treatment strategy that provides substantial, but less than absolute, symptom control. Traditionally, healing of erosive esophagitis has been an important outcome measure in reflux patients to prevent long-term complications. However, healing of esophagitis is usually accompanied by relief of heartburn, and conversely, persistence of erosions is often associated with an unacceptable level of symptoms. Thus, even in erosive reflux disease, symptom relief can be seen as the most important outcome measure.

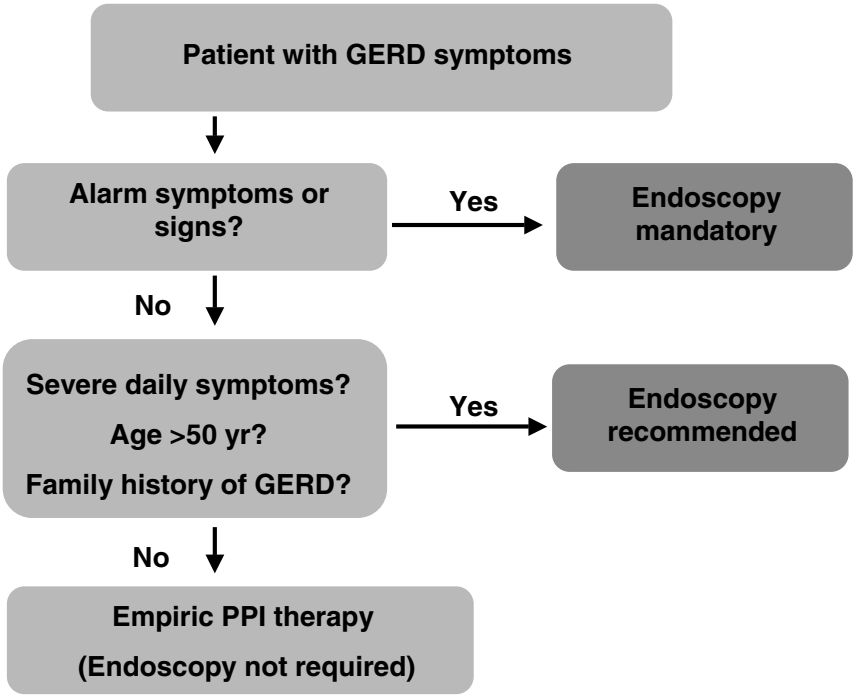

Figure 2. Diagnostic algorithm for patients with GERD to determine which patients require upper endoscopy.

SELECTING PATIENTS FOR ENDOSCOPY

For patients presenting with symptoms suggestive of GERD, a major decision point is whether or not to perform an upper endoscopy (Fig. 2). Endoscopy is mandatory for all patients presenting with alarm symptoms—dysphagia, unintended weight loss, signs of gastrointestinal bleeding, or anemia. For patients who have not undergone previous investigation, some experts would recommend an endoscopy if the patient is aged 50 yr or older, has a family history of reflux disease, or has severe and/or continuous symptoms on a daily basis (47). This recommendation is based on clinical experience rather than solid evidence from prospective studies. Antisecretory therapy should be held for at least 2 wk in patients undergoing endoscopy to prevent it from masking erosive disease and even upper gastrointestinal carcinomas (41). Patients who are known to be infected with *H. pylori* should be endoscoped or have eradication therapy before deciding on further management. All other patients can be treated empirically with a PPI for 2–4 wk. If successful, the patient can be instructed to continue with on-demand dosing. Endoscopy should be considered in patients failing initial therapy, in patients who experience a change in clinical profile, or when the patient uses medication on a frequent basis. The value of routine endoscopy in nonendoscoped patients who are successfully managed with on-demand therapy with only a few symptomatic relapses a year is probably very low.

EMPIRICAL TREATMENT

Although current clinical guidelines support empirical therapy in patients with reflux symptoms but no alarm symptoms, there are some controversial issues in the proposed algorithm: First, the outcome of empirical PPI therapy will not distinguish a patient with reflux disease from a patient with peptic ulcer. However, reflux esophagitis is by far the most common organic diagnosis in dyspeptic patients presenting in primary care and a peptic ulcer is found in only 5% of patients, even in a population with a 30% *Helicobacter* prevalence (48). The concept of empirical therapy was supported in a recent 6-month trial comparing continuous therapy with on-demand dosing in uninvestigated patients. Even though the on-demand group had more frequent and severe symptoms, the rating of overall effect on heartburn control of the regimens did not differ between the groups (49). Second, in patients managed without an initial endoscopy, daily dosing for 4 wk—and not on-demand therapy—is recommended before a decision about further management is made. Some of these patients will have erosive reflux disease and the chance of complete healing increases with increasing treatment length. Although studies suggest that symptom response is a useful indicator of healing, this has only been documented in trials with at least 2–4 wk of therapy. Furthermore, an extended initial treatment phase increases the chance of symptom response. In this way, more patients will experience complete absence of heartburn and these patients will have a useful "internal" standard of the best possible care with which to compare future therapies (46). Finally, the first treatment episode may differ from all the rest because patients who consult for reflux symptoms have usually had their symptoms for a long time. This increases the likelihood of erosions being present, as opposed to subsequent episodes, where the patient can take the medication as soon as symptoms recur and thereby,

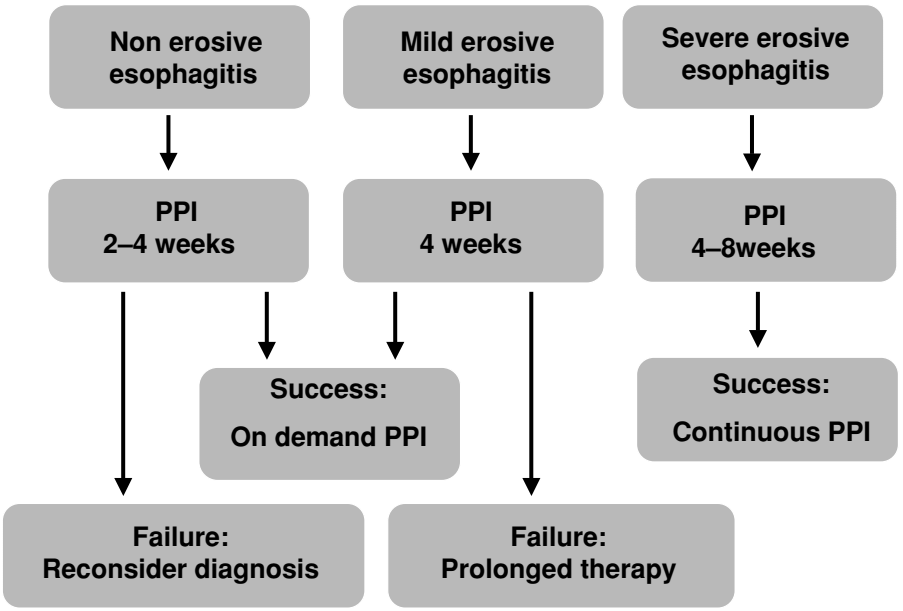

Figure 3. Therapeutic algorithm for patients with GERD according to endoscopic findings.

hopefully, prevent mucosal damage. Recent studies have suggested that microscopic esophagitis is very common in nonerosive reflux disease (50). Evidently, reflux-related mucosal damage is a biological continuum from minor microscopic alterations in some patients to erosions and ulcerations in others. However, there is little evidence indicating that nonerosive reflux disease will progress if symptoms are allowed to recur and are treated on an as-needed basis. Data on the long-term prognosis and risk of complications in reflux disease are scarce and based on studies preceding the widespread use of PPIs, but suggest that the prognosis is very good (36, 51). However, it should be acknowledged that certain authorities maintain that all indivduals on long-term maintenance PPI therapy have one upper endoscopy to exclude significant underlying disease (*i.e.*, Barrett's esophagus) and this may pertain to on-demand therapy as well.

SELECTING LONG-TERM THERAPY FOR ENDOSCOPED PATIENTS

Patients with severe esophagitis (*e.g.*, Los Angeles grades C and D), those with Barrett's esophagus, and those with extra-esophageal manifestations should not be considered for on-demand therapy. Patients in all other subgroups, including those with a normal endoscopy and those with mild erosive disease (Los Angeles grades A and probably grade B as well) are potential candidates for on-demand therapy (Fig. 3). For patients with mild, uncomplicated erosive esophagitis, initial treatment should consist of a 4-wk course of standard-dose PPI, and if successful, then patients may be prescribed on-demand PPI therapy (47). If symptoms persist after initial therapy, then PPI therapy should be given for an additional 4–8 wk. When symptoms persist after the initial PPI course for nonerosive or mild erosive disease, clinicians should consider another diagnosis, possible compliance issues, or the possibility of PPI-refractory disease.

The recommendation of on-demand therapy for patients with mild erosive reflux disease is controversial and to date there is little evidence from clinical trials (43, 44, 52). In support, European investigators found that more than 90% of actively treated patients were willing to continue therapy for 6 months in a trial with 439 patients with nonerosive or mild erosive disease comparing pantoprazole with placebo on-demand (43). In line with this, less than 5% of patients with erosive esophagitis withdrew from a long-term study due to symptoms (44). On the other hand, once-daily PPI therapy was superior to on-demand dosing for keeping patients with erosive disease in endoscopic remission. However, patients were equally satisfied and symptomatic relapse rates did not differ. Using on-demand dosing, 78% and 65% of patients with Los Angeles grades A and B, respectively, were in endoscopic remission at 6 months (52).

Reprint requests and correspondence: David C. Metz, M.D., Division of GI, 3 Ravdin, 3400 Spruce Street, Philadelphia, PA 19104.
Received August 4, 2006; accepted September 26, 2006.

REFERENCES

1. Sontag SJ. The medical management of reflux esophagitis. Role of antacids and acid inhibition. Gastroenterol Clin North Am 1990;19:683–712.
2. Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002;122:1500–11.
3. Henke CJ, Levin TR, Henning JM, et al. Work loss costs due to peptic ulcer disease and gastroesophageal reflux disease in a health maintenance organization. Am J Gastroenterol 2000;95:788–92.

4. Boath EH, Blenkinsopp A. The rise and rise of proton pump inhibitor drugs: Patients' perspectives. Soc Sci Med 1997;45:1571–9.
5. Hungin AP, Rubin G, O'Flanagan H. Factors influencing compliance in long-term proton pump inhibitor therapy in general practice. Br J Gen Pract 1999;49:463–4.
6. Hungin AP, Rubin GP, O'Flanagan H. Long-term prescribing of proton pump inhibitors in general practice. Br J Gen Pract 1999;49:451–3.
7. Harris RA, Kuppermann M, Richter JE. Prevention of recurrences of erosive reflux esophagitis: A cost- effectiveness analysis of maintenance proton pump inhibition. Am J Med 1997;102:78–88.
8. Goeree R, O'Brien B, Hunt R, et al. Economic evaluation of long-term management strategies for erosive oesophagitis. Pharmacoeconomics 1999;16:679–97.
9. Gerson LB, Robbins AS, Garber A, et al. A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. Am J Gastroenterol 2000;95:395–407.
10. Wahlqvist P, Junghard O, Higgins A, et al. Cost effectiveness of proton pump inhibitors in gastro-oesophageal reflux disease without oesophagitis: Comparison of on-demand esomeprazole with conventional omeprazole strategies. Pharmacoeconomics 2002;20:267–77.
11. Meineche-Schmidt V, Juhl HH, Ostergaard JE, et al. Costs and efficacy of three different esomeprazole treatment strategies for long-term management of gastro-oesophageal reflux symptoms in primary care. Aliment Pharmacol Ther 2004;19:907–15.
12. Hansen AN, Wahlqvist P, Jorgensen E, et al. Six-month management of patients following treatment for gastroesophageal reflux disease symptoms—a Norwegian randomized, prospective study comparing the costs and effectiveness of esomeprazole and ranitidine treatment strategies in a general medical practitioners setting. Int J Clin Pract 2005;59:655–64.
13. Remak E, Brown RE, Yuen C, et al. Cost-effectiveness comparison of current proton-pump inhibitors to treat gastro-oesophageal reflux disease in the UK. Curr Med Res Opin 2005;21:1505–17.
14. Hughes DA, Bodger K, Bytzer P, et al. Economic analysis of on-demand maintenance therapy with proton pump inhibitors in patients with non-erosive reflux disease. Pharmacoeconomics 2005;23:1031–41.
15. Johnston DA, Wormsley KG. The effect of food on ranitidine-induced inhibition of nocturnal gastric secretion. Aliment Pharmacol Ther 1988;2:507–11.
16. Merki HS, Halter F, Wilder-Smith C, et al. Effect of food on H_2-receptor blockade in normal subjects and duodenal ulcer patients. Gut 1990;31:148–50.
17. Misiewicz JJ. Clinical relevance of tolerance to peptic ulcer healing and relapse. Aliment Pharmacol Ther 1990;4(suppl 1):85–96.
18. Nwokolo CU, Smith JTL, Gavey C, et al. Tolerance during 29 days of conventional dosing with cimetidine, nizatidine, famotidine or ranitidine. Aliment Pharmacol Ther 1990;4(suppl 1):29–46.
19. Nwokolo CU, Prewett EJ, Sawyerr AFM, et al. Tolerance during 5 months of dosing with ranitidine 150 mg nightly: A placebo-controlled, double-blind study. Gastroenterology 1991;101:948–53.
20. Smith JTL, Gavey C, Nwokolo CU, et al. Tolerance during 8 days of high-dose H_2-blockade: Placebo-controlled studies of 24-h acidity and gastrin. Aliment Pharmacol Ther 1990;4(suppl 1):47–64.
21. Wilder-Smith CH, Ernst T, Gennoni M, et al. Tolerance to oral H_2-receptor antagonists. Dig Dis Sci 1990;35:976–83.
22. Lachman L, Howden CW. Twenty-four hour intragastric pH: Tolerance within five days of continuous ranitidine administration. Am J Gastroenterol 2000;95:57–61.
23. Jones DB, Howden CW, Burget DW, et al. Alteration of H_2-receptor sensitivity in duodenal ulcer patients during maintenance treatment with an H_2-receptor antagonist. Gut 1988;29:890–3.
24. Prewett EJ, Hudson M, Nwokolo CU, et al. Nocturnal intragastric acidity during and after a period of dosing with either ranitidine or omeprazole. Gastroenterology 1991;100:873–7.
25. Smith AD, Gillen D, Cochran KM, et al. Dyspepsia on withdrawal of ranitidine in previously asymptomatic volunteers. Am J Gastroenterol 1999;94:1209–13.
26. Sachs G, Shin J-M, Howden CW. Clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 2006;23(suppl 2):2–8.
27. Lee TJ, Fennerty MB, Howden CW. Systematic review: Is there excessive use of proton pump inhibitors in gastro-oesophageal reflux disease? Aliment Pharmacol Ther 2004;20:1241–51.
28. Sobrino-Faya M, Igelsias-Rey M, Dominguez-Munoz E. On-demand maintenance therapy in patients with esophagitis and non-erosive reflux disease (NERD): A prospective, randomized, crossover, comparative study of rabeprazole versus lansoprazole [abstract]. Gastroenterology 2006;130:A-177.
29. Hepburn B, Goldlust B. Comparative effects of an omeprazole antacid complex–immediate release (OAC-IR) and omeprazole delayed-release (OME-DR) on omeprazole pharmacokinetics and gastric pH in healthy subjects [abstract]. Gastroenterology 2003;124:A228.
30. Howden CW. Immediate release proton-pump inhibitor therapy–potential advantages. Aliment Pharmacol Ther 2005;22(suppl 3):25–30.
31. Castell D, Bagin R, Goldlust B, et al. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2005;21:1467–74.
32. Katz PO, Ballard DE, Koch FK, et al. Nocturnal gastric acidity alter bedtime doping of proton pump inhibitors in patients with nighttime GERD symptoms [abstract]. Gastroenterology 2006;130:A-175.
33. Andersson K, Carlsson E. Potassium-competitive acid blockers: A new approach to acid suppression. Gastroenterol Hepatol Annu Rev 2006;1:118–22.
34. Kahrilas PJ, Dent J, Lauritsen K, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis [abstract]. Gastroenterology 2006;130:A-174.
35. Dent J, Kahrilas P, Hatlebakk J, et al. A randomized, comparative efficacy study of three doses of AZD0865 and esomeprazole in patients with non-erosive reflux disease [abstract]. Gastroenterology 2006;130:A-176.
36. Vakil N, van Zanten S, Kahrilas P, et al. The Montreal definition and classification of gastro-esophageal reflux disease (GERD)—A global evidence-based consensus. Am J Gastroentrol 2006;101:900–20.
37. Zacny J, Zamakhshary M, Sketris I, et al. A systematic review of the efficacy of intermittent and on-demand therapy with histamine H_2-receptor antagonists or proton pump inhibitors for GERD patients. Aliment Pharmacol Ther 2005;21:1299–1312.

38. Armstrong D, Marshall JK, Chiba N, et al. Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults—update 2004. Can J Gastroenterol 2005;19:15–35.
39. Zacny J, Sketris I, Skedgel C, et al. Utilization of antisecretory medication in 100,000 Nova Scotia seniors' pharmacare beneficiaries between 1998 and 2002: A cohort database analysis. Gastroenterology 2004;126 (suppl 2):W1277.
40. Junghard O, Carlsson R, Lind T. Sufficient control of heartburn in endoscopy-negative gastro-oesophageal reflux disease trials. Scand J Gastroenterol 2003;38:1197–9.
41. Moayeddi P. Dyspepsia: Managing dyspesia in adults in primary care. 2004. http://www.nice.org.uk/page.aspx?o=CG017.
42. Scholten T, Dekkers CP, Schutze K, et al. On-demand therapy with pantoprazole 20 mg as effective long-term management of reflux disease in patients with mild GERD: The ORION trial. Digestion 2005;72:76–85.
43. Kaspari S, Kupcinskas L, Heinze H, et al. Pantoprazole 20 mg on demand is effective in the long-term management of patients with mild gastro-oesophageal reflux disease. Eur J Gastroenterol Hepatol 2005;17:935–41.
44. Johnsson F, Moum B, Vilien M, et al. On-demand treatment in patients with oesophagitis and reflux symptoms: Comparison of lansoprazole and omeprazole. Scand J Gastroenterol 2002;37:642–7.
45. Johannessen T, Petersen H, Kristensen P, et al. The intensity and variability of symptoms in dyspepsia. Scand J Prim Health Care 1993;11:50–5.
46. Bytzer P. Goals of therapy and guidelines for treatment success in symptomatic gastroesophageal reflux disease patients. Am J Gastroenterol 2003;98(suppl):S31–9.
47. Bytzer P, Blum AL. Personal view: Rationale and proposed algorithms for symptom-based proton pump inhibitor therapy for gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2004;20:389–98.
48. Thomson AB, Barkun AN, Armstrong D, et al. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: The Canadian Adult Dyspepsia Empiric Treatment - Prompt Endoscopy (CADET-PE) study. Aliment Pharmacol Ther 2003;17:1481–91.
49. Morgan DG, O'Mahony MF, O'Mahony WF, et al. Maintenance therapy with continuous and on-demand rabeprazole 20 mg in uninvestigated gastroesophageal reflux disease. Gastroenterology 2006;130:A174.
50. Zentilin P, Savarino V, Mastracci L, et al. Reassessment of the diagnostic value of histology in patients with GERD, using multiple biopsy sites and an appropriate control group. Am J Gastroenterol 2005;100:2299–306.
51. Isolauri J, Luostarinen M, Isolauri E, et al. Natural course of gastroesophageal reflux disease: 17–22 year follow-up of 60 patients. Am J Gastroenterol 1997;92:37–41.
52. Sjostedt S, Befrits R, Sylvan A, et al. Daily treatment with esomeprazole is superior to that taken on-demand for maintenance of healed erosive oesophagitis. Aliment Pharmacol Ther 2005;22:183–91.

CONFLICT OF INTEREST

Guarantor of the article: David C. Metz, M.D.
Specific author contributions: David C. Metz: Conceived the symposium, invited the other contributors, conceived the manuscript combined the contributions into a single publication.
John M. Inadomi: Performed the economic analysis and was primary author for this section.
Colin W. Howden: Was primary author for the pharmacology section.
Sander J. V. van Zanten: Performed the clinical analysis and was primary author for this section.
Peter Bytzer: Was primary author for the recommendations section.
Financial support: None
Potential competing interests: David C. Metz: Consultant - AstraZeneca, Wyeth, TAP, Eisai, Altana; Honoraria-AstraZeneca, Wyeth, Santarus; Research-TAP, AstraZeneca, Wyeth.
John M. Inadomi: Consultant - AstraZeneca; Honoraria - TAP, Novartis
Colin W. Howden: Consultant - Santarus, Takeda, Novartis, Eisai, Schwartz Valeant, TAP; Honoraria: AstraZeneca, Santarus, Novartis.
Sander J. V. van Zanten: Consultant - AstraZeneca, Johnson & Johnson, Abbott, Altana, GlaxoSmithKline; Honoraria-AstraZeneca, Johnson & Johnson, Abbott; Research: Abbott, Altana
Peter Bytzer: None