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RESEARCH ARTICLE

Guidance on the use of over-the-counter proton pump inhibitors for the treatment of GERD

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Abstract *Objective* The aim of this paper was to develop a guideline on the over-the-counter management of gastroesophageal reflux disease with proton pump inhibitors (i.e. omeprazole). *Setting* A meeting of internationally renowned gastroenterologists in January 2009, in Berlin, Germany. *Methods* An expert panel group of gastroenterologists convened to develop a consensus-based algorithm for pharmacists for over-the-counter (OTC) treatment with proton pump inhibitors (PPIs). Key considerations were the short-term safety and efficacy of PPIs, and the extent of the risk to the sufferer, owing to the treatment not being controlled by a physician. *Main outcome measures* A consensus-based treatment algorithm for the OTC management of gastroesophageal reflux disease and evidence-based guidance on the use of OTC PPIs. *Results* As defined by the treatment algorithm, the pharmacist should first confirm the diagnosis based on the presence of typical symptoms and secondly, as a result, rule out general practitioner referral. The third step focuses on the nature, severity and frequency of the symptoms—the patients who might have the highest benefit from a short course (14 days) of OTC PPIs are those with less than three episodes of heartburn and/or acid regurgitation per week. Patients who have three or more episodes per week can use the OTC PPIs but should also be encouraged to visit a physician, and those who already have a diagnostic work-up can use proton pump inhibitors as rescue treatment if they are known responders. Guidance for pharmacists, in the form of questions and answers, summarises the current published clinical experience with PPIs in terms of their efficacy and safety, and optimal treatment schedule. *Conclusions* Gastroesophageal reflux disease imposes a considerable burden on sufferers. Owing to their accepted efficacy and safety, PPIs are becoming popular as OTC options for the treatment of gastroesophageal reflux disease symptoms such as heartburn and acid regurgitation. Effective self-management of gastroesophageal reflux disease with OTC PPIs, e.g. omeprazole, could lead to lasting freedom from symptoms and improved quality of life for sufferers.

Keywords Gastroesophageal reflux disease · GERD · Guidance · Omeprazole · OTC drugs · Pharmacist · Proton pump inhibitors

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Impact of findings on practice

- The switch to over-the-counter proton pump inhibitors will necessitate the need for pharmacists to gain greater awareness of the efficacy and safety profiles of these agents.
- The development of a consensus-based treatment algorithm offers a clinical point of reference for

community pharmacists to guide and tailor their decisions on the self-management of gastroesophageal reflux disease with over-the-counter proton pump inhibitors.

Introduction

Gastroesophageal reflux disease (GERD) is defined by a reflux of stomach contents into the oesophagus that increases acidic exposure to the oesophageal mucosa and causes troublesome symptoms [1, 2]. More than half of sufferers state 'symptoms that are too uncomfortable to bear' as their reason for seeking medical advice [3]. Heartburn (retrosternal burning) is a typical presenting symptom of GERD, but acid regurgitation is also a frequent symptom among sufferers. Heartburn is estimated to affect 24% of sufferers on at least a daily basis, while 43% experience heartburn once or twice per week [4]. Importantly, the presentation of heartburn and acid regurgitation together predicts a diagnosis of GERD with greater than 90% accuracy [5]. Most sufferers (80%) also have at least one extraoesophageal symptom, including wheezing, chronic cough, shortness of breath or unexplained chest pain [5]. Sufferers with warning symptoms such as dysphagia, weight loss, choking, early satiety or frequent vomiting require urgent medical advice and diagnostic work-up, as these symptoms may be a sign of adenocarcinoma, Barrett's oesophagus or other severe conditions [5].

Reflux disease is very common worldwide, with higher prevalence in Europe and the US (10–20%) than Asia (2.5–4.8% in China) [6, 7]. The prevalence of GERD symptoms is increasing, and the condition is particularly common among the elderly and those with a high body mass index (BMI) (>25 kg/m^2) [8–10]. The burden of GERD is considerable, with a significant negative effect on quality of life [11]. Sufferers frequently report eating and sleeping disturbances, but GERD symptoms also have adverse effects on work and social activities [11]. In a study examining the GERD sufferer's perspective, symptom improvement was a key expectation from treatment (>90% of sufferers) [12].

Alongside lifestyle changes, several medications are available for the management of GERD, including antacids, alginates, histamine-2 receptor antagonists (H_2-RAs), and proton pump inhibitors (PPIs) [13, 14]. The superiority of the PPIs over placebo in patients with GERD is well accepted [14]. Also, PPIs show an advantage over H_2-RAs for symptomatic response and healing [14, 15].

A number of existing medications have demonstrated efficacy for the management of GERD symptoms in the OTC setting [16]. As a result of their established long-term safety and efficacy, there have also been increasing efforts to switch PPIs from prescription to OTC treatment [17].

Worldwide, several consensus groups have developed treatment guidelines for the management of GERD [18–22]; however, there is inconsistency with respect to the first-line management approach (either diagnostic work-up or medication first) and treatment duration in cases where medication is recommended first (varies from 1 to 8 weeks). Although the switch from prescription to OTC status is growing, this has not translated to specific recommendations on OTC treatment in recent evidence-based guidelines for the management of GERD [20, 23].

Aim of the study

The aim of this study was to develop guidance for pharmacists on the OTC management of GERD with PPIs.

Method

An expert panel group of gastroenterologists (Holtman G, Bigard M-A, Malfertheiner P and Pounder R) convened in January 2009 with the aim of developing a guidance on the OTC management of GERD with PPIs (omeprazole). Expert members agreed that current GERD treatment guidelines are centered on the approach by the physician and therefore there is a need to develop specific guidance that brings the patient into the centre of the care and decision-making process, bearing in mind that the switch to OTC will mean a greater responsibility for the pharmacist. In developing a consensus-based algorithm for the OTC treatment of GERD with PPIs, key considerations were the short-term safety and efficacy of PPIs (the long-term effectiveness of PPIs is well documented) and the extent of the risk to the sufferer because of a treatment that is not controlled by a physician. Consensus was reached through discussion of current evidence and on the basis of clinical experience of the expert group. To support the algorithm, an evidence-based reference guide on the use of OTC PPIs was developed in the form of questions and answers, with the intention that the article can be used as a quick reference guide for community pharmacists.

Results

Treatment algorithm

A consensus-based treatment algorithm for the OTC management of GERD is presented in Fig. 1.

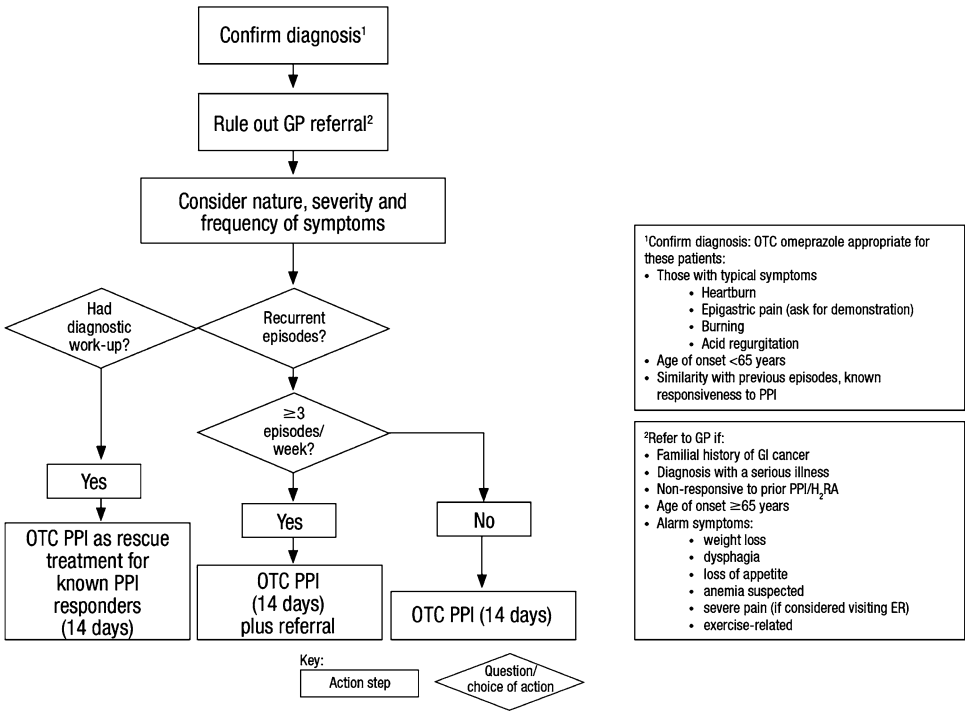

Fig. 1 Consensus treatment algorithm for the OTC management of GERD with PPIs. *OTC* over-the-counter, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor, *GP* general practitioner, *H_2-RAs* histamine-2 receptor antagonists

On the basis of clinical experience, the expert panel recommended the following patient advice to be used alongside the algorithm: (a) the onset of action of PPIs is not as immediate as that of antacids but will be sustained; (b) the time of dose should be when symptoms are likely to occur; e.g. if a patient mostly experiences nocturnal heartburn, they should take their medication in the evening; (c) most will achieve complete resolution of symptoms within 2–3 days; (d) symptoms might return when the medication is stopped.

Guidelines for pharmacists

Clinical experience regarding the switch from prescription (Rx) to OTC omeprazole

Responsible use, as directed, and rapid relief from complaints among sufferers taking OTC omeprazole has been reported. Responsible handling and use of OTC omeprazole according to the US Food and Drug Administration (FDA)-approved indication and package information leaflet was shown in 758 US sufferers who self-administered with OTC omeprazole (maximum duration of treatment was 14 days) [24]. Approximately 97% of sufferers treated heartburn as directed by the package insert.

A 14-day comparative study of OTC famotidine versus omeprazole in 32 patients demonstrated similar efficacy in terms of gastric acid suppression between the two treatments on Day 1, but OTC omeprazole was superior to famotidine thereafter [25]. Relief of GERD symptoms with OTC omeprazole occurs rapidly. In 1,024 patients with frequent heartburn, about 50% had complete relief from symptoms with OTC omeprazole 20 mg [26].

Experience with the switch from prescription H_2-RAs to self-medication

Overall, the number of physician visits does not decrease because of the switch from Rx to OTC H_2-RA treatment [27]. This evidence suggests a low risk of masking symptoms, as physician examinations will take place in the case of persistent complaints. Therefore it can be surmised that the number of physician visits for acid-related complaints is likely to remain the same even after relatively new medications—such as H_2-RAs in the past and PPIs in the future—are released for self-medication.

Benefits of an OTC–PPI treatment compared with current/previous OTC options

Existing OTC treatments have specific advantages and disadvantages; selection of the most appropriate should be made on an individual patient basis.

Antacids are associated with rapid, symptomatic relief, but they have a brief duration of action [28] and therefore would need to be taken frequently throughout the day to provide efficient relief of symptoms. They have a

predominantly local effect by neutralising gastric acid but do not influence the amount of acid produced.

H_2-RAs inhibit histamine-induced gastric acid production and are effective for the relief of typical GERD symptoms [16]. They have a longer duration of action compared with antacids but are not as effective as PPIs for oesophagitis associated with GERD [29]. Development of tachyphylaxis has been observed, even during short-term therapy [30]. This class effect manifests as a loss of acid inhibitory efficacy and is present within a few doses but does not progress after 29 days [30].

PPIs are the most effective treatment for GERD symptoms. Indeed, a recent meta-analysis reported that PPIs are the most effective agents for the treatment of GERD compared with other OTC options [14]. PPIs show stronger and longer acid suppression than H_2-RAs [31–35]. Acid suppression lasts up to 24 h with PPIs versus 3 and 15 h with antacids and H_2-RAs, respectively [36–38]. PPIs have an early onset of action (acid suppression approximately 1.5 h after administration; comparable with H_2-RAs) that manifests clinically within 1–3 days [31, 39–45]. The efficacy and tolerability of PPIs (omeprazole) results in greater improvements in quality of life than with H_2-RAs [46].

Is 14-day treatment duration sufficient? What is the recommendation for a sufferer with recurrent relapses?

Clinical evidence supports the efficacy of PPIs when administered for 14 days [25, 26, 31, 43, 44, 47]. In one study of 1,024 patients with frequent heartburn, 14-day treatment with omeprazole resulted in complete resolution of symptoms in approximately 50% of patients [26]. Sufficient relief or complete freedom from complaints is seen after an average of 1–3 days' treatment with PPIs in the majority of cases [26, 31, 44]. Unlike the H_2-RA famotidine, OTC omeprazole is associated with a therapeutic effect that lasts for more than 14 days of treatment [24, 26], with some patients free of symptoms for 10 weeks [24].

Insufficient relief on 2 weeks of treatment or recent recurrent relapses

Patients experiencing persistent symptoms even after treatment should be advised to seek further medical advice [4].

When is sustained gastric acid reduction required? Is this better managed under a physician's control?

Sufferers requiring sustained acid reduction may be those with frequently recurring symptoms, younger patients (<65 years), and those whose dominant symptom is heartburn [17].

Physician-led management of treatment is recommended when there are alarm symptoms or if the complaints persist beyond the stated application period or if they worsen or immediately recur, as indicated in the Patient Information Leaflet [48].

Optimal administration schedule for an OTC PPI

PPIs should be taken at the time of day when symptoms are commonly experienced. Most patients will experience complete relief within 2–3 days of administration [49].

When should the medications be taken? Close to the time of symptom experience (personal communication, Expert group), e.g. if the patient mostly experiences symptoms during the day, advise them to take the medicine in the morning, e.g. before breakfast. If the patient mostly experiences symptoms at night, advise them to take their medication at night, preferably before supper.

When should the patient expect to experience relief after taking the first tablet? Most patients will respond to PPI therapy within 1–3 days of treatment. A systematic review of 18 studies has shown that 31 and 35% of patients achieve complete heartburn relief as early as within 1 and 2 days of PPI treatment, respectively [49].

When will the maximum effect be achieved and what factors influence the response to therapy? Maximum acid suppression with PPIs is seen after approximately 3–5 days [50]. In a study of 509 patients who received omeprazole (10 or 20 mg daily) or placebo for 4 weeks, 31 and 46% of omeprazole-treated patients for the 10 or 20 mg groups, respectively, had complete resolution of their symptoms of heartburn compared with 13% of the placebo group [51]. Patients with higher levels of exposure to acid before treatment had a better response in the study. Higher age, male gender and a greater number of heartburn episodes were linked to higher levels of oesophageal acid exposure [51].

For maximum effect, omeprazole should be taken before a meal [52]; otherwise, the onset of action may be delayed and increase the risk of treatment failure.

Is there any risk of continuous self-medication (beyond 14 days) with PPI?

Continuous administration is a cause for concern only in the presence of alarm symptoms (weight loss, blood in the faeces, and frequent and possibly haemorrhagic vomiting), which may suggest a severe illness. As a standard,

pharmacists should advise patients to seek medical advice if alarm signs are present and if symptoms persist after 14 days of treatment. Respective warnings can also be found in the Patient Information Leaflet [48].

Patients generally seek physician advice when they have persistent complaints [53]. A physician consultation was determined by: (1) increase in frequency and intensity of the complaints; (2) insufficient control of symptoms and their effects on daily life; (3) fear of a severe illness; and (4) desire for a diagnosis. In 2,000 patients experiencing heartburn, two-thirds of respondents with recurring or persisting symptoms sought physician advice at least once [54]. In another survey, however, most physicians (87%) reported infrequent or no persistence of GERD symptoms after treatment with PPIs [55].

Lack of prompt and complete response to any empirical reflux treatment indicates that further investigation is needed—a fact also mentioned as a warning in the Patient Information Leaflet [48]. Non-response to empiric treatment has been the focus of treatment guidelines [22, 56], concluding that (a) initial empirical treatment will only result in a short delay in the confirmation of the diagnosis (days to a few weeks); and (b) this delay is not considered to influence the prognosis in the case of an advanced neoplasm. Therefore, there is a low risk of masking symptoms in the self-management of GERD.

For a customer reporting typical heartburn and acid regurgitation, is there a significant risk of a life-threatening condition?

Which symptoms suggest a life-threatening condition that requires diagnostic work-up without delay? Patients with typical symptoms and co-occurring alarm symptoms, as listed below, should seek urgent medical advice to exclude the presence of a serious condition:

- Dysphagia
- Unintended, significant weight loss
- Bleeding
- Choking
- Early satiety
- Frequent vomiting

The above-mentioned alarm symptoms may suggest malignancy, stricture or ulceration. Their presence prompts urgent medical advice and diagnostic work-up [5, 6]. The American College of Gastroenterology suggest that diagnostic work-up (upper endoscopy) should be a consideration for patients with chronic symptoms and those who do not respond to empiric treatment [18]. Heartburn that occurs during exercise may point towards cardiovascular disease rather than an acid-related disorder.

Ulcers, Barrett's Oesophagus and other severe gastric disorders An initial course of self-medication with a PPI does not exclude a diagnostic work-up in the event of persistent complaints. Therefore, if symptoms persist, a consultation with a physician is recommended.

Peptic ulcers and lesions are commonly linked to *Helicobacter pylori* infection or non-steroidal anti-inflammatory drugs (NSAIDs) [57]. In GERD sufferers with erosive oesophagitis (20% of all GERD patients), less than 5% had ulcers or strictures [58].

Chronic GERD as a risk factor for Barrett's Oesophagus (BO) is increasingly being called into question [59]. Among 300 patients over 65 years of age who were referred for colonoscopy, the detection rate of BO was unrelated to previously reported GERD symptoms [60]. Approximately 1% of GERD patients developed BO over follow-up periods of 2–3.4 years in large clinical studies [61, 62].

Additional risk factors for BO include advanced age, male gender, Caucasian ethnicity or smoking, as well as genetic disposition [59, 61]. Also, the detection of BO after reflux oesophagitis may frequently relate to the unmasking of a pre-existing condition once the oesophagitis has healed [63].

Less than 1% of people with BO develop oesophageal adenocarcinoma each year [64]. The low prevalence of oesophageal adenocarcinoma compared with the high occurrence of reflux symptoms results in a low absolute risk of this type of cancer among patients with GERD [65].

Thus, the risk of BO is unlikely to be a relevant concern for pharmacists administering advice to patients with GERD symptoms. However, if symptoms are frequent and severe in spite of OTC omeprazole therapy, patients should be referred to their physician anyway.

Does PPI use increase the risk of infectious disorders?

Acid suppression may be associated with a slightly increased risk of gastrointestinal (GI) infections [66]. Acid in the stomach acts as disinfectant, thus further studies are needed to confirm a possible association between acid suppression and the risk of enteric infections. An increase in pH depends on the dose and length of consecutive administrations. With PPI treatment, the gastric pH also occasionally falls into the weakly acidic range ($pH < 3$), which is enough to extensively destroy pathogens [66, 67]. Patients taking PPIs should be advised of the potential risk of infectious diseases, especially when travelling abroad. A retrospective analysis of medical records has suggested that PPI use during treatment for *Clostridium difficile* infection (CDI) may be associated with a higher risk of recurrent CDI, but the extent of this risk is higher in people aged

over 80 years and those who have not received the correct antibiotic treatment for the infection [68].

Drug interactions or other relevant side effects of PPI

PPIs might influence the absorption and concentration in the blood of coumarins, benzodiazepines, hexobarbital, antidepressants, digoxin, clarithromycin, antimycotics (e.g. ketoconazole) and vitamin B12 [69]. Omeprazole can reduce the levels of the active form of clopidogrel in the blood and reduce its antiplatelet effects [70, 71].

A summary of FDA-reported adverse events and drug interactions occurring during therapy with omeprazole, lansoprazole and pantoprazole revealed that vitamin K antagonist interactions were by far the most common but the total frequency was low [72]. The low frequency indicated that there was not a major clinical risk from any such interaction.

What are the side effects of PPI treatment? PPIs are well tolerated [73]. However, side effects might occur in a small number of users. Common side effects (occurring in $\geq$1–10% of patients) are:

- Diarrhoea
- Headache
- Nausea
- Abdominal pain
- Constipation

Are there additional risks associated with PPI treatment? Over the long term (average follow-up period of 7.8 years), use of PPIs was shown to be modestly associated with some types of fractures in postmenopausal women [74].

Discussion

GERD imposes a considerable burden on sufferers [3]. Owing to their accepted efficacy and safety, PPIs are becoming popular as OTC options for the treatment of GERD symptoms such as heartburn and acid [17]. Recent clinical guidelines have generally overlooked recommendations for OTC management [19, 22]. An expert group was convened to develop a consensus-based algorithm for the OTC management of GERD with PPIs and the outcomes of those discussions are reported here.

Formal consensus and hierarchical analytical methods were not adopted for the development of the treatment algorithm. However, in creating the management pathway and evidence-based question and answer guidance for pharmacists presented herein, the intention was to address the current unmet clinical need for an OTC management pathway for GERD.

The algorithm should serve as a foundation for replication in more formal guideline recommendations. Moreover, the utility of this treatment algorithm may be explored in a future survey-based study of community pharmacists.

Conclusion

The outputs from this specifically convened meeting of an expert group of gastroenterologists should be helpful to guide PPI use in the OTC setting. Effective self-management of GERD with OTC PPIs, e.g., omeprazole, could lead to lasting freedom from symptoms and improved quality of life for GERD sufferers.

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