Gastro-oesophageal reflux: An overview of the cost-effectiveness of pharmacotherapeutic treatment options

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Abstract

Gastro-oesophageal reflux disease (GORD) produces symptoms that cause great irritation to the patient. Pharmacotherapeutic management is directed at minimising these symptoms and reducing the causative factors, e.g. acid production, thereby providing relieve. Currently available agents include simple antacids and acid suppression therapy, including histamine 2-receptor antagonists, proton pump inhibitors, mucosal or cytoprotective agents, pro-motility agents. Deciding on appropriate therapy will be dependent on the diagnosis, side-effects and cost-effectiveness of the treatment.

Keywords: GORD, gastro-oesophageal reflux, PPIs, proton-pump inhibitors, cost-effectiveness

Introduction

Patients who suffer from gastro-oesophageal reflux disease (GORD) suffer from acid heartburn (dyspepsia) due to the reflux of stomach acid into the distal part of the oesophagus. Drug management is aimed at decreasing the amount of stomach acid that enters the distal oesophagus, usually by increasing the rate at which the stomach empties into the duodenum, and relieving the discomfort caused by the heartburn. From a treatment perspective, however, the distinction between the management of GORD and peptic ulceration is purely arbitrary. Both are acid peptic diseases that are characterised by inflammatory and erosive changes in the normal gut mucosa. Both require an essentially similar pharmacotherapeutic treatment approach

Pharmacotherapy

The pharmacological management of GORD may consist of one or more of the following treatment options, either alone, sequentially, or in combination:[1-4]

- Simple antacids
- Acid-suppression therapy
- Mucosal or cytoprotective agents
- Pro-motility agents.

Simple antacids

Simple antacids, such as those containing aluminium and magnesium, neutralise the hydrochloric acid in the stomach and are quite effective as pain relievers. The magnesium-containing antacids cause diarrhoea, while the aluminium-containing ones cause constipation. The combination of magnesium and aluminium will therefore constitute the antacid of choice

(e.g. a combination of aluminium hydroxide and magnesium trisilicate). The divalent cations (i.e. Al^{2+} and Mg^{2+}), however, would interact with chelating agents, such as the tetracycline and fluoroquinolone antimicrobials, and several other drug interactions are possible.[3,4]

Combining an antacid with an alginate may actually prevent reflux, in that the alginate literally forms a floating gel on top of the gastric contents. Calcium carbonate and sodium bicarbonate may also be used as simple antacids. However, care should be taken with these agents, since calcium carbonate may interfere with normal acid-base balance and cause metabolic alkalosis, or it may elicit rebound gastric acid secretion, making it suitable for short-term use only. Meanwhile sodium bicarbonate should be used with caution in patients who require a restricted sodium intake.[3,4]

Dimethicone and simethicone may relieve a 'bloated feeling' by acting as antiflatulent or defoaming agents. They may also be of benefit in the management of intestinal colic in infants and children. However, they do not contribute to the efficacy of the acid neutralisation brought about by the antacids.[3,4]

Acid-suppression therapy

Drugs that increase gastric pH fall into two categories, namely the histamine2-receptor antagonists (H_2RAs) and the proton-pump inhibitors (PPIs), with the latter group constituting the most effective drugs by far.[1,3,4]

Histamine 2-receptor antagonists

Blocking the gastric H_2-receptors of parietal cells will reduce stomach acid secretion. These agents are highly selective,
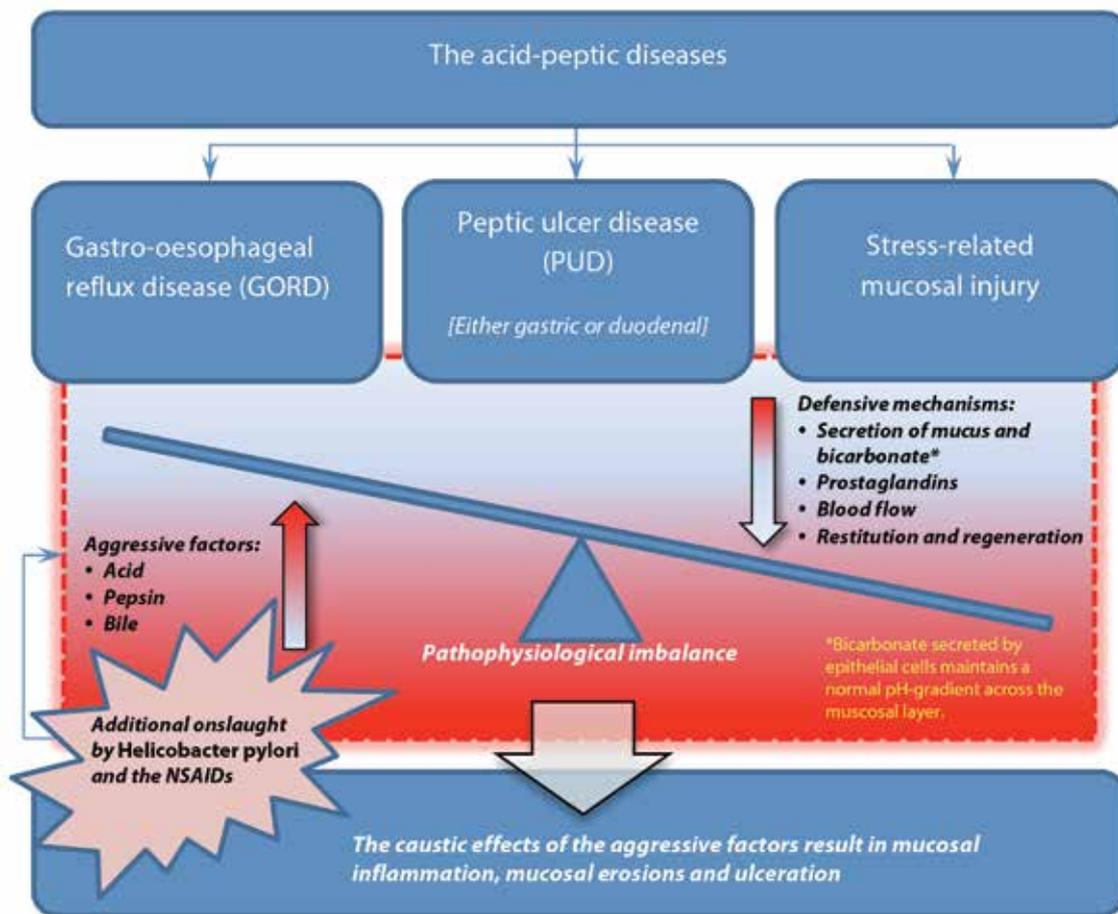
Figure 1: The acid-peptic diseases and their resultant mucosal injury (common contributors to the pathological imbalance between the aggressive factors and the normal defence mechanisms are infections with *Helicobacter pylori* and the use of non-steroidal anti-inflammatory drugs, or NSAIDs. The latter two aggravating factors contribute to nine in 10 cases of peptic ulceration).[1]

competitive inhibitors, capable of suppressing both basal and food-induced acid secretion from these cells, albeit more modestly for the latter and making them less ideal for day-time acid suppression. Ulcer healing rates are significant but not nearly as good as those obtained through the use of the PPIs. In patients with erosive oesophagitis the H_2-blockers are only effective in fewer than 50% of cases. Cimetidine, ranitidine, famotidine and nizatidine are examples of these selective histaminergic-receptor blockers. Cimetidine has the disadvantage of sometimes producing unwanted antiandrogenic side-effects in male patients (it has a fairly small affinity for androgen receptors). It also has a higher likelihood of multiple drug interactions through its inhibition of cytochrome P450 isozymes. These agents are especially useful in the suppression of nocturnal acid secretion, which largely depends on the physiological actions of histamine.[1,3,4]

Proton-pump inhibitors (PPIs)

These drugs enter the parietal cells of the gastric glands, found in the gastric pits of the stomach lining, where they subsequently and irreversibly inhibit the H^+/K^+-ATPase pump (i.e. the proton pump that is specifically responsible for the H^+-secretion into the lumen of the gastric pits where these cations combine with the secreted Cl^- from a separate pump to form HCl). This effectively prevents the secretion of gastric acid from the gastric pits into the lumen of the stomach.[1,3,4]

Therefore, these drugs are highly effective in increasing the stomach pH, rapidly relieving the symptoms and achieving good cure rates. They are administered as pro-drugs and are very widely used because of their established, favourable efficacy and safety profiles. Currently-available examples of PPIs are omeprazole, esomeprazole (the *S*-isomer of omeprazole), lansoprazole, pantoprazole and rabeprazole. The PPIs are still the most effective agents in the management of both non-erosive and erosive GORD, as well as the complications of reflux disease.[1,3,4]

Mucosal or cytoprotective agents

These drugs are referred to as cytoprotective because they protect the cells of the stomach lining against the corrosive effects of stomach acid. In addition, misoprostol also promotes perfusion of the gastric mucosa because it is an analogue of prostaglandin E_1 (PGE_1).

Sucralfate forms a protective layer that covers the exposed surface of the ulcer and, in doing so, produces cure rates that are comparable to those obtained with the H_2-receptor antagonists. It should preferably be taken one hour before meals, since it is activated by stomach acid. The viscous paste will cover exposed ulcer or erosive surfaces for up to six hours. Wherever sucralfate is combined with any of the simple antacids, the antacid should be taken half an hour after taking the sucralfate (i.e. on an empty stomach as well).[1,3,4]

Misoprostol is of particular use in preventing the gastrotoxic effects of the non-steroidal anti-inflammatory drugs (NSAIDs). It influences the ratio of acid-to-mucus secretion favourably by increasing gastric mucus secretion while decreasing acid secretion. Care should be taken with this drug, however, since PGE_1 causes uterine contractions, it may be used for termination of pregnancy or the induction of labour, and should therefore be avoided during pregnancy.[1,3,4]

Bismuth compounds may also be used, and may have a variety of beneficial effects, some of which are yet to be fully elucidated. These include the formation of a protective barrier by coating ulcers and erosions in the mucosal lining, stimulating the secretion of mucus, bicarbonate and prostaglandins, as well as its ability to act as an antimicrobial and to bind enterotoxins (hence its usefulness in the management of traveller's diarrhoea and to help eradicate *Helicobacter pylori*).[1]

Pro-motility agents

Metoclopramide acts as an agonist at gastrointestinal $5-HT_4$-receptors, thus increasing the rate of gastric emptying and peristalsis. Domperidone has a similar mechanism of action, but differs from metoclopramide in that it does not cross the blood-brain barrier. Cisapride is another $5-HT_4$-receptor agonist, which is unrelated to the abovementioned two drugs. It has the disadvantage of causing potentially serious cardiac side-effects, such as ventricular dysrhythmias (by causing QT_c-interval prolongation), especially when its own metabolism is inhibited (through various drug interactions, for instance). Access to this drug has been restricted and it should be used with extreme caution.[1,3,4]

Bethanechol is a parasympathomimetic drug, which selectively stimulates muscarinic receptors (of the M_3-subtype). In the gastrointestinal tract this causes smooth muscle contraction, but produces relaxation of the sphincters. Bethanechol therefore stimulates the functional contraction of the gastrointestinal tract (i.e. it increases intestinal motility). A different approach with a similar outcome on the motility of the GIT would be to use neostigmine. Erythromycin also has pro-kinetic properties. It acts as a direct stimulator of the motilin receptors.[1,3]

The usefulness of these agents in GORD is limited, with metoclopramide and domperidone being reserved for patients with regurgitation and refractory heartburn.[1]

Cost-effectiveness

Cost-effectiveness analysis

Health-related expenditures comprise of direct costs and indirect costs. Direct costs are the medical costs of obtaining and providing treatment, while indirect costs include costs that result from the disease but are not related to the provision of health care, e.g. time lost from work due to illness.[5] When different management strategies for a disease are compared, the cost of each strategy must be balanced against its effectiveness.[5] It is important that the cost-effectiveness of treatment is considered in conjunction with its therapeutic effectiveness.[6] The ideal

situation would be to increase the therapeutic effectiveness of treatment at a lower cost than the standard or current therapy.[5] In practice though, this will be highly unlikely and the best balance between increased costs and effectiveness must be established to maximise outcomes within the constraints of available resources.[5]

A cost-effectiveness analysis (CEA) is the primary pharma-coeconomic tool that is used to compare the costs of a health intervention with the expected health benefits or a common therapeutic goal.[2,6] With a CEA health outcomes are expressed in common units so that comparisons among different treatments can be made, with a ratio of benefits measured in therapeutic effects per money unit of expenditure.[5,6] A simple cost comparison between the different oral, acid-lowering agents on the local market (with a specific indication and dosage recommendation for reflux oesophagitis, as part of GORD) is provided in Table 1.

Cost-effective treatment options for GORD

Gastro-oesophageal reflux disease (GORD) is a chronic condition, with symptoms having a marked effect on patients' work performance and health-related quality of life (QoL). Patients continuously experience symptomatic relapse and often require continued therapy.[5,7,8] Untreated GORD could have a more negative impact on a patient's psychological well-being, than many other chronic conditions, such as hypertension.[2] These factors all contribute to GORD being an expensive condition to manage, with both direct and indirect costs to the patient.[5]

The primary objectives for the treatment of GORD are to relieve the symptoms, to heal injury, and to prevent recurrences and complications. Each of these predicted outcomes are associated with different costs and can have an effect on the patient's QoL. The cost-effectiveness of therapy for the treatment of GORD must therefore be calculated in terms of the predicted outcomes as well as the effects on the patient's quality of life. When a treatment is ineffective, it is considered as the most expensive therapy, regardless of whether it is actually less expensive than its comparator, because additional costs are incurred when retreatment is required.[2]

Locally, the PPIs are generally more expensive than the H_2-antagonists for the treatment of GORD (see Table 1). There is no doubt about the superiority of the PPIs over other agents, as the most effective therapy in the management of GORD and the associated complications of reflux disease, in terms of clinical endpoints.[2] Evidence from CEAs showed that PPIs are more cost-effective than H_2-receptor antagonists, particularly in patients with moderate to severe GORD.[2,5,8] Amongst the class of PPIs, cost-effectiveness comparisons, including various outcome measures, such as annual costs, number of symptom-free days and quality-adjusted life-years, illustrated the relative cost-effectiveness of specific PPIs in the treatment and maintenance of GORD and erosive reflux oesophagitis.[8,9,10]

Table 1: Cost comparison between the different oral, acid-lowering agents on the local market (with a specific indication and dosage recommendation for reflux oesophagitis, as part of GORD)

H_2-receptor antagonists (H_2-blockers):			
	As indicated for reflux oesophagitis	**Cost per pack**	**Cost of the recommended dosage per month (30 days)**
Cimetidine:			
Adco-Cimetidine®	400 mg QID (120 tablets per month)	400 mg, 60, R33.91	For 120 tablets: R 67.82
Bio-Cimetidine®	400 mg QID (120 tablets per month)	400 mg, 56, R 24.12	For 112 tablets: R 48.24
Hexamet®	400 mg QID (120 tablets per month)	400 mg, 60, R 49.18	For 120 tablets: R 98.36
Lenamet®	400 mg QID (120 tablets per month)	400 mg, 56, R 24.84	For 112 tablets: R 49.68 (A pack size of 500 is also available for R 221.81)
Secadine®	400 mg QID (120 tablets per month)	400 mg, 60, R 31.92	For 120 tablets: R 63.84
Ranitidine:			
CPL Alliance Ranitidine®	150 mg BID, or 300 mg nocte	150 mg, 60, R 40.21 300 mg, 30, R 20.89	For 30 tablets: R 20.89
Histak®	150 mg BID, or 300 mg nocte	150 mg, 60, R 52.91 300 mg, 30, R 35.28	For 30 tablets: R 35.28
Ranihexal®	150 mg BID, or 300 mg nocte	150 mg, 10, R 17.56 300 mg, 30, R 42.94	For 30 tablets: R 42.94 (A 150 mg tablet pack size of 300 is also available for R 527.01)
Ranit®	150 mg BID, or 300 mg nocte	150 mg, 60, R 48.47 300 mg, 30, R 32.79	For 30 tablets: R 32.79
Ranitidine 300 Biotech®	150 mg BID, or 300 mg nocte	300 mg, 30, R 40.78	For 30 tablets: R 40.78
Ultak®	150 mg BID, or 300 mg nocte	150 mg, 60, R 65.64 300 mg, 30, R 54.35	For 30 tablets: R 54.35
Zantac®	150 mg BID, or 300 mg nocte	150 mg, 60, R 533.58 300 mg, 30, R 504.07	For 30 tablets: R 504.07 (Effervescent tablets are also available in both strengths)
Proton-pump inhibitors (PPIs):			
Omeprazole:			
Adco-Omeprazole®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 28, R 123.44	For 28 capsules: R 123.44 For 56 capsules: R 246.88
Altosec®	20 mg daily (dosage range of 10 to 40 mg daily)	10 mg, 28, R 120.96 20 mg, 28, R 121.29	For 28 capsules: R 121.29 For 56 capsules: R 242.58
Lokit®	20 mg daily (dosage range of 10 to 40 mg daily)	20 mg, 30, R 121.08	For 30 capsules: R 121.08 For 60 capsules: R 242.16
Losec®	20 mg daily (dosage range of 10 to 40 mg daily)	10 mg, 28, R 290.48 20 mg, 28, R 484.98 40 mg, 14, R 424.00	For 28 MUPS tablets: R 290.48 For 28 MUPS tablets: R 484.98 For 28 MUPS tablets: R 848
Omez®	20 mg daily (**dosage range of 10 to 40 mg daily**)	10 mg, 30, R 130.93 20 mg, 30, R 131.65 40 mg, 30, R 242.93	For 30 capsules: R 130.93 For 30 capsules: R 131.65 For 30 capsules: R 242.93
Sandoz Omeperazole®	20 mg daily (dosage range of 10 to 40 mg daily)	20 mg, 30, R 113.31	For 30 capsules: R 113.31 For 60 capsules: R 226.62
Lansoprazole:			
Adco-Roznal®	30 mg daily (15 mg daily to prevent relapse)	15 mg, 28, R 144.22 30 mg, 28, R 101.31	For 28 capsules: R 101.31
Aspen Lansoprazole®	30 mg daily (15 mg daily to prevent relapse)	15 mg, 30, R 122.70 30 mg, 30, R 181.51	For 30 capsules: R 181.51
Lancap®	30 mg daily (15 mg daily to prevent relapse)	15 mg, 30, R 76.80 30 mg, 30, R 107.94	For 30 capsules: R 107.94
Lansoloc®	30 mg daily (15 mg daily to prevent relapse)	30 mg, 30, R 173.31	For 30 capsules: R 173.31
Lansoprazole Unicorn®	30 mg daily (15 mg daily to prevent relapse)	15 mg, 30, R 111.34 30 mg, 30, R 131.80	For 30 capsules: R 131.80
Lansoprazole-Winthrop®	30 mg daily (15 mg daily to prevent relapse)	15 mg, 28, R 151.96 30 mg, 28, R 216.82	For 28 capsules: R 216.82
Lanzor®	30 mg daily (15 mg daily to prevent relapse)	15 mg, 28, R 294.03 30 mg, 28, R 477.64	For 28 capsules: R 477.64

Pantoprazole:			
Aspen Pantoprazole®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 30, R 109.86 40 mg, 30, R 163.17	For 30 tablets: R 109.86 For 30 tablets: R 163.17
Conoran®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 30, R 82.77 40 mg, 30, R 131.33	For 30 tablets: R 82.77 For 30 tablets: R 131.33
Gastriwin®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 28, R 147.23 40 mg, 28, R 219.91	For 28 tablets: R 147.23 For 28 tablets: R 219.91
Mylan Pantoprazole®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 30, R 83.91 40 mg, 30, R 130.61	For 30 tablets: R 83.91 For 30 tablets: R 130.61
Pantocid®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 30, R 116.86 40 mg, 30, R 173.57	For 30 tablets: R 116.86 For 30 tablets: R 173.57
Pantoloc®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 28, R 193.74 40 mg, 28, R 365.57	For 28 tablets: R 193.74 For 28 tablets: R 365.57
Pentoz®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 30, R 108.49 40 mg, 30, R 161.15	For 30 tablets: R 108.49 For 30 tablets: R 161.15
Peploc®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 28, R 106.81 40 mg, 28, R 158.89	For 28 tablets: R 106.81 For 28 tablets: R 158.89
Topzole®	20 mg daily (up to 40 mg daily in refractory cases)	20 mg, 28, R 153.38 40 mg, 28, R 228.00	For 28 tablets: R 153.38 For 28 tablets: R 228.00
Rabeprazole:			
Pariet®	10-20 mg daily (20 mg daily for erosive oesophagitis)	10 mg, 28, R 139.37 20 mg, 28, R 278.65	For 28 tablets: R 139.37 For 28 tablets: R 278.65
Rabemed®	10-20 mg daily (20 mg daily for erosive oesophagitis)	10 mg, 28, R 100.12 20 mg, 28, R 200.95	For 28 tablets: R 100.12 For 28 tablets: R 200.95
Esomeprazole:			
Nexiam®	20 mg daily (40 mg daily for erosive oesophagitis)	20 mg, 28, R 290.95 40 mg, 28, R 448.71	For 28 MUPS tablets: R 290.95 For 28 MUPS tablets: R 448.71

[Unit prices are based on the current, local single-exit drug pricing data-base.]

Long-term pharmcotherapy

Safety is always a concern with any long-term pharmacotherapy.[11] Although the PPIs are very effective in the treatment of GORD, with a low incidence of side-effects, continued use may have potential long-term consequences, which in turn can increase healthcare costs.[11,12,13] Malabsorption and risk of infections are the two main concerns with chronic PPI use.[11] Decreased absorption of two key minerals, calcium (hypocalcaemia) and magnesium (hypomagnesaemia), could lead to bone fractures, especially hip fractures, and cardiac abnormalities.[11,12] Data also suggest the potential risk of variations in the bioavailability of common medications and vitamin B_{12} deficiency.[8] *Clostridium difficile*-associated diarrhoea and community-acquired pneumonia are infections most commonly associated with long-term PPI therapy.[11,12] To maximise the cost-effectiveness of treatment and to ensure minimal risk, a step-down, step-off, or on-demand PPI therapy approach may be considered.[12] Caution should be exercised with the specific approach in respect of patients who need chronic treatment for conditions such as erosive esophagitis, as this condition may reduce the effectiveness of the treatment itself.[13,14] On the other hand, patients with no indication for long-term therapy are exposed to these long-term risks.[12]

Adherence and persistence to medication

Adherence to medication is known to be a strong predictor of the outcome of therapy and is related to the costs of therapy. Less complicated, once-daily treatment regimens improve adherence, compared to multi-dose regimens and/or higher-dosage regimens, which could also be more expensive.[2,13] Retrospective cohort study data on adherence and persistence to PPI therapy for various conditions indicated that 75% of patients who start PPI therapy stop treatment within one year. Non-continuous (intermittent or on-demand) use of PPIs was evident amongst half of all patients, which may lead to decreased drug use and cost savings for patients who are treated only for symptom control. However, intermittent or on-demand PPI use, would be insufficient for patients with GORD, which requires continuous maintenance use.[13] Adherence monitoring and investigation of sub-optimal adherence and persistence to PPI therapy for these patients could be useful, prior to considering alternative management options such as anti-reflux surgery (ARS).[15]

Anti-reflux surgery

Anti-reflux surgery (ARS), most commonly laparoscopic fundoplication, is an alternative management strategy to long-term medication use, which is associated with pill-burden, medication expenses and reduced QoL.[15] Various literature, including a Cochrane meta-analysis, a systematic review and a number of clinical trials that evaluated the long-term health benefits, cost-benefits and cost-effectiveness of ARS, in comparison to continued pharmacotherapeutic management, reported ARS to be equal or superior to PPI therapy in controlling reflux-related symptoms, at least in the short to medium term.[15,16] A more recent retrospective, population-based register study in Denmark showed a greater-than-50% risk of long-term

supplemental PPI therapy five years after ARS.[15] Physicians and patients should be aware of the risk and subsequent implications of long-term PPI therapy, needed to achieve sufficient relief of symptoms following anti-reflux surgery.[15]

The benefits of effective pharmacotherapy and the improvement in QoL for patients with GORD significantly outweigh the potential adverse effects and risks in most patients.[12] Clinicians should be sensitive to the fact that patients with no indication for long-term pharmacotherapy are only exposed to the risks of such treatment, in addition to unnecessary cost expenditure.[12] Cost-effectiveness analyses can play an important role in supporting decision-making with regard to healthcare priorities in South Africa, with its constrained healthcare resources. Evidence from CEA provides useful information for prescribing in clinical practice as well as policy guidance at the patient level, service level and population level.[17]

Conclusion

In the management of GORD various agents and classes of agents are available, either for management of the symptoms, or for the treatment thereof. It has been shown that the PPI's are more effective than the histamine-2 receptor antagonists in managing GORD, and are also superior to placebo in patients with GORD symptoms. Specific drug selection within the PPI group, should be based on individual adverse effects profiles, the expected onset of action, and the cost of treatment. The availability of generic dosage forms of the PPIs makes these drugs a more cost-effective option for the management of GORD.

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