Gastro-oesophageal reflux – an overview

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Abstract

Gastro-oesophageal reflux disease (GORD) presents with patients experiencing discomfort due to acid-containing stomach contents persistently being refluxed into the oesophagus. This condition can lead to serious complications if left untreated. The two chief complaints of GORD are heartburn and regurgitation. The management of GORD is wide and varied and includes antacids, H2-antagonists, alginates, pro-kinetics, or proton pump inhibitors. GORD is known to cause economic and social burdens, thus appropriate management is vital to improving a patient's quality of life.

Keywords: GORD, heartburn, regurgitation, acid suppression

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Introduction

Gastro-oesophageal disease (GORD) is defined as the persistent exposure of reflux of the stomach contents into the oesophagus and oral cavity that results in discomfort and/or complications.[1,2] GORD is a common complaint in medical practices and interventions such as lifestyle changes, life-long medication or invasive surgery are warranted. Globally, the increasing economic and social burden of GORD has placed the condition under the spotlight. It was estimated that annually, £760 million and approximately $24 billion in the UK and USA respectively, were lost to productivity and healthcare costs with respect to GORD.[3] Furthermore, GORD has been associated with a lower quality of life and poor sleep patterns.[2]

GORD may be aggravated by various comorbidities and risk factors. GORD can be classified into three different categories namely; physiological gastro-oesophageal reflux, pathological gastro-oesophageal reflux and secondary oesophageal reflux.

Management of GORD 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 heartburn.[4-6] The two chief symptoms that present in GORD are heartburn and regurgitation.[2] Heartburn is a burning sensation in the centre of the chest that can spread to the throat and can occur approximately 30–60 minutes after a large meal. Additionally, experiencing heartburn 2–3 times a week may be a clear indicator of GORD.[7,8]

Epidemiology

GORD is not age specific but mainly occurs in people older than 40 years. Prevalence of GORD varies, with the highest incidence being observed in Western countries. Mortality is rare and gender only plays a significant role in the development of Barrett's oesophagus but not for GORD. Risk factors and comorbidities that may worsen or even contribute to GORD are listed in Table I.[2]

Pathophysiology

GORD develops when there is abnormal reflux of gastric contents from the stomach into the oesophagus. A defective lower oesophageal sphincter pressure (LESP) is the main pathophysiologic mechanism. Other normal mucosal defence mechanisms contributing to GORD include; abnormal oesophageal anatomy, improper oesophageal clearance of gastric fluids, reduced mucosal resistance to acid, delayed or ineffective gastric emptying, inadequate production of epidermal growth factor, and reduced salivary buffering of acid.[9]

Clinical presentation

The presumptive diagnosis of GORD is made in the presence of typical symptoms (heartburn, regurgitation and dysphagia) occurring two or more times a week in patients under the age of 50 with no other symptoms.[10]

Heartburn: retrosternal burning sensation/discomfort behind the breastbone occurring after meals, bending over or lying supine.

Regurgitation: spontaneous return of gastric and/or oesophageal contents into the pharynx. Respiratory complications can arise due to regurgitation of gastric content into the tracheobronchial tree.

Dysphagia: One-third of patients experience dysphagia, feeling a sensation of food stuck mainly in the retrosternal area.

Atypical symptoms include coughing, chest pain, and wheezing. Complications such as oesophagitis, stricture and Barret oesophagus may occur, and these patients should be referred for further diagnostic testing if they do not respond to therapy.[11]

In 50% of cases, reflux causes non-cardiac chest pain and patients present to the emergency department thinking that they are

Table I: Risk factors for GORD [2,7]

	Risk factors for GORD
	**Hiatus hernia** Hiatus hernia (HH) is when the junction between the oesophagus and the stomach (the gastroesophageal junction) is dislodged. This junction prevents the stomach content from refluxing into the oesophagus. Patients with HH have regular episodes of reflux.
	**Obesity** People who have central adiposity are more likely to present with GORD as there is increased gastric pressure resulting in the change in pressure gradient at the oesophageal and stomach junction resulting in reflux.
	**High-fat diet** Consuming a high-fat diet is more likely to cause GORD compared to a low-fat diet.
	**Tobacco smoking** Smoking increases stomach acid production and weakens the lower oesophageal sphincter increasing the risk of reflux. Furthermore, saliva is a neutraliser and smoking reduces saliva production, further increasing the risk of GORD.
	**Alcohol consumption** Alcohol has shown to increase stomach acid production and lower oesophageal pressure. Seven or more alcoholic drinks per week have been shown to be a risk factor for GORD.
	**Genetics** Genetics have been shown to cause GORD.
	**Medications** Nonsteroidal anti-inflammatory drugs, antibiotics (e.g. tetracyclines and clindamycin), statins, angiotensin-converting enzyme inhibitors, bisphosphonates, vitamin C, potassium, iron, clomipramine, quinidine, anticholinergics, tricyclic antidepressants, corticosteroids (oral and inhaled), β-agonists, nitroglycerines, aminophylline, benzodiazepines, warfarin, cyproterone, ethinylestradiol, and calcium channel blockers have all been linked to GORD.
Other risks	Food and drinks such as coffee, chocolate, citrus, spicy food and tomatoes can all potentially increase the risk for GORD.

having a myocardial infarction. To rule out a cardiac cause, a 24-hour pH testing can be done or an oesophageal manometry. A high dose of a proton pump inhibitor (PPI) can be alternatively used.[11]

Classification of GORD

GORD is classified into three categories:

1. Physiological (or functional) gastro-oesophageal reflux: no underlying factors or conditions are present with normal growth and development. Pharmacologic treatment is generally not necessary unless lifestyle changes are not successful.
2. Pathological gastro-oesophageal reflux: patients who are regularly experiencing above mentioned symptoms, requiring evaluation and treatment.
3. Secondary gastro-oesophageal reflux: where an underlying condition predisposes gastro-oesophageal reflux.

Pharmacist management of GORD

GORD is characterised by inflammatory and erosive changes in the normal gut mucosa. The treatment approach to patients with dyspeptic symptoms, as for acid heartburn and GORD, is aimed at:[6,12]

- Decreasing the amount of stomach acid that enters the distal oesophagus, usually by neutralising stomach acid, decreasing the production of hydrochloric acid (HCl), increasing the rate at which the stomach empties into the duodenum, and
- relieving the discomfort caused by the heartburn.

The major drug target sites in current practice settings include the proton pump (or the H+-K+-ATPase pump), the gastric H2-receptor and the gastrointestinal 5-HT4-receptor. These targets may be supported by the simple antacids and the prostaglandin analogues. The pharmacotherapeutic measures may be strengthened by adhering to basic, non-pharmacological intervention strategies.

The treatment of GORD should be individualised, with the goal being the alleviation of symptoms, decreasing the frequency of recurrent disease, promoting the healing of mucosal injury and the prevention of complications[10]

Patients with life-threatening symptoms such as:[13]

- dysphagia
- unintended, significant weight loss
- bleeding
- choking
- early satiety
- frequent vomiting

need to be referred to a doctor immediately.

History taking[2]

Before diagnosing GORD and initiating over-the-counter treatment, pharmacists must rule out any reason for a referral to a doctor. Therefore, taking a detailed history is important. Table II includes some of the questions and responses that forms part of a detailed history.

Non-pharmacological interventions

Dietary recommendations and lifestyle modifications should be individualised for each patient. It is recommendable for patients to refrain from indulging in foods that could trigger the onset of dyspeptic symptoms, such as fats, alcohol, peppermint and spearmint. These foods may decrease LESP or increase transient lower oesophageal sphincter relaxation. Spicy foods, orange juice, tomato juice and coffee have a direct irritant effect on the oesophageal mucosa. Smaller meals should also rather be taken more frequently to avoid unnecessary gastric distension.

Patients should also be advised to avoid the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other medications with a strong link to the occurrence of dyspepsia, wherever possible. If an NSAID must be used, then the patient should also be given preventative therapy to avoid uncomfortable dyspeptic symptoms.[10,14-16]

Other non-pharmacological measures can include

- Elevating the head end of the bed, which increases oesophageal clearance as well as the pH; may be done with 15–20 cm blocks placed underneath the head-side of the bed.
- Weight loss in obese patients (reduces symptoms).
- Including protein-rich meals in the diet (augments LESP).
- Avoiding food intake at least two hours before sleeping, especially when nocturnal symptoms are present.
- Smoking cessation.
- Taking medication in the upright sitting position with enough liquid.

Pharmacological interventions

The pharmacological management of GORD should be orientated towards the clinical presentation of the disease and symptom intensity. Table III provides an overview of the different oral, acid-lowering agents on the local market (with a specific indication and dosage recommendation for reflux oesophagitis, as part of GORD), It may consist of one or more of the following treatment options, either alone, sequentially, or in combination:[6,10,12,14,17]

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

Table II: History taking

Questions	GORD-related responses
What is the age of the patient?	Refer older patients (> 65 years) who present with GORD symptoms to the doctor
What symptoms are you experiencing?	Burning sensation that begins in the midpoint of the abdomen and rising toward the throat Rising of food into throat/mouth
What worsens your symptoms	Large meal Fatty meal Stooping/bending, etc.
How severe are your symptoms?	Mild/moderate/severe
Are there any unrelated GORD symptoms that you may be experiencing? (Important for pharmacists to record as patients may not associate symptoms with GORD)	Darkened bowel motions Vomiting blood Crushing chest pain Diagnosed/suspected anaemia Frequent vomiting Weight loss Difficulty swallowing Severe abdominal pain Exercise-related symptoms Feeling full after eating small amounts
Do you have any other health conditions?	Gastric ulcer Cancer
What treatment/s have you already tried, and have they worked?	Antacids/alginate Histamine H2 receptor antagonists Proton pump inhibitors

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. Al2+ and Mg2+), however, would interact with chelating agents, such as the tetracycline and fluoroquinolone antimicrobials, and several other drug interactions are possible.[6,12]

Combining an antacid with an alginate may actually prevent reflux, in that the alginate literally forms a floating gel above 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.[6,12]

Dimethicone- and simethicone-containing agents 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, and there is no evidence supporting their chronic use.[6,10,12]

Acid-suppression therapy

Drugs that increase gastric pH fall into two categories, namely histamine2-receptor antagonists (H2RAs) and PPIs, with the latter group constituting the most effective drugs by far.[6,]

Histamine 2-receptor antagonists

Blocking the gastric H2-receptors of parietal cells will reduce stomach acid secretion. These agents are highly selective, inhibitors capable of suppressing both basal- and food-induced acid secretion from these cells, albeit more modestly for the latter, making them less ideal for daytime acid suppression. Ulcer healing rates are significant but not nearly as good as those obtained through the use of PPIs. In patients with erosive oesophagitis, the H2RAs 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.[6,12,17]

Proton pump inhibitors

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.[6,12,17]

Therefore, these drugs are highly effective in increasing the stomach pH, rapidly relieving 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. PPIs are best taken 30 minutes before breakfast, as a greater quantity of active pumps is available during that time of the day. Currently-available examples of PPIs are omeprazole, esomeprazole (the *S*-isomer of omeprazole), lansoprazole, pantoprazole and rabeprazole. 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.[6,10,12,17]

There is growing evidence that PPIs come with adverse reactions/risks. The risk of *Clostridium difficile* infections and pneumonia have found to be increased when using PPIs. Furthermore, osteoporosis and impaired magnesium metabolism are also concerns that prescribers need to be aware of with PPI usage.[18]

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 E1 (PGE1).

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 H2-receptor antagonists. It should preferably be taken one hour before meals, since it is activated by stomach acid. The viscous paste will cover exposed ulcers 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).[6,12,17]

Misoprostol is of particular use in preventing the gastrotoxic effects of 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 PGE1 causes uterine contractions, it may be used for termination of pregnancy or the induction of labour, and should therefore be avoided during pregnancy.[6,12,17]

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*).[17]

Pro-motility agents

Metoclopramide acts as an agonist at gastrointestinal 5-HT4-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-HT4-receptor agonist unrelated to the two abovementioned drugs. It has the disadvantage of causing potentially serious cardiac side effects, such as ventricular dysrhythmias (by causing QTc-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.[6,12,17]

Bethanechol is a parasympathomimetic drug which selectively stimulates muscarinic receptors (of the M3-subtype). In the gastrointestinal tract (GIT), this causes smooth muscle contraction, but produces relaxation of the sphincters. Bethanechol, therefore, stimulates the functional contraction of the GIT (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.[6,17]

Table III: Acid-lowering agents with indication and adverse drug reactions[18,20-22]

	As indicated for reflux oesophagitis	Adverse drug reactions
H_2-receptor antagonists (H_2-blockers):		
Cimetidine		
Adco-Cimetidine®	400 mg QID (120 tablets per month)	Use with caution in renal and hepatic impairment Diarrhoea, dizziness, tiredness, rash, headache **Drug interactions** *Albendazole: increases levels of albendazole and cimetidine *Do not use artemether-lumefantrine with cimetidine *Carbamazepine: raised levels of cimetidine and risk of carbamazepine side effects with cimetidine
Bio-Cimetidine®		
Hexamet®		
Lenamet®		
Secadine®		
Ranitidine		
CPL Alliance Ranitidine®	150 mg BID, or 300 mg nocte	As above
Histak®		
Ranihexal®		
Ranit®		
Ranitidine 300 Biotech®		
Ultak®		
Zantac®		
Proton pump inhibitors (PPIs)		
Omeprazole		
Adco-Omeprazole®	20 mg daily (up to 40 mg daily in refractory cases)	Gastrointestinal tract disturbances, angioedema, fever, alopecia, insomnia, gynaecosmastia, blurred vision, thrombocytopaenia, liver enzyme changes. Prolonged use can alter the absorption of vitamin B12 and iron and the metabolism of calcium and magnesium. Osteoporosis, increased risk of pneumonia and *clostridium difficile* infections have also been seen with prolonged use of PPIs. Omeprazole may cause impotence and agitation, while pantoprazole can cause raised serum triglycerides and cholesterol. **Drug interactions** *Clarithromycin: increased levels of clarithromycin and omeprazole *Clopidogrel: reduced effect of clopidogrel and thus best avoided *Citalopram: raised levels of citalopram and omeprazole *Theophylline: reduced levels of lansoprazole and theophylline – use with caution
Altosec®	20 mg daily (dosage range of 10 to 40 mg daily)	
Lokit®		
Losec®		
Omez®		
Sandoz Omeperazole®		
Lansoprazole		
Adco-Roznal®	30 mg daily (15 mg daily to prevent relapse)	As above
Aspen Lansoprazole®	30 mg daily (15 mg daily to prevent relapse)	
Lancap®		
Lansoloc®		
Lansoprazole Unicorn®		
Lansoprazole-Winthrop®		
Lanzor®		
Pantoprazole		
Aspen Pantoprazole®	20 mg daily (up to 40 mg daily in refractory cases)	As above
Conoran®		
Gastriwin®		
Mylan Pantoprazole®		
Pantocid®		
Pantoloc®		
Pentoz®		
Peploc®		
Topzole®		
Rabeprazole		
Pariet®	10–20 mg daily (20 mg daily for erosive oesophagitis)	As above
Rabemed®		
Esomeprazole		
Nexiam®	20 mg daily (40 mg daily for erosive oesophagitis)	As above

The usefulness of these agents in GORD is limited, with metoclopramide and domperidone being reserved for patients with regurgitation and refractory heartburn.[17]

Special population

Pregnant women

GORD is a common presentation (45-80%) amongst pregnant women, with heartburn being the main complaint. This is mainly due to hormonal or mechanical factors. As mentioned, the LOS pressure is responsible for the movement of the stomach content between the oesophagus and the stomach and during pregnancy the increasing oestrogen and progesterone results in a decreased LOS pressure. Furthermore, the increasing abdominal pressure also poses a risk of GORD. Lifestyle changes, which include reducing the intake of offending foods, such as spicy foods should be recommended. GORD is treated as a step-up therapy in pregnant women, with antacids introduced as the first step in management followed by PPIs.[19]

Conclusion

With the increasing economical and social burden associated with GORD, physicians and other health care professionals should be aware of the condition and its treatment strategies. In the management of GORD, there is a plethora of options available, either for management of the symptoms, or for the treatment thereof.

It has been shown that PPIs are more effective than H2RAs in managing GORD, and are also superior to placebo in patients with GORD symptoms. However, the adverse risks associated with PPIs must be considered and based on individual adverse effects profiles and the expected onset of action.

References

1. Sharma P, Yadlapati R. Pathophysiology and treatment options for gastroesophageal reflux disease: looking beyond acid. Ann N Y Acad Sci. 2021;1486(1):3-14. https://doi.org/10.1111/nyas.14501.
2. MacFarlane B. Management of gastroesophageal reflux disease in adults: a pharmacist's perspective. Integr Pharm Res Pract. 2018;7:41-52. https://doi.org/10.2147/IPRP.S142932.
3. Nirwan JS, Hasan SS, Babar ZU, Conway BR, Ghori MU. Global prevalence and risk factors of gastro-oesophageal reflux disease (GORD): systematic review with meta-analysis. Sci Rep. 2020;10(1):5814. https://doi.org/10.1038/s41598-020-62795-1.
4. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. 11th ed. The McGraw-Hill Companies, Inc. China; 2009.
5. Dipiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy – A pathophysiologic approach. 8th ed. The McGraw-Hill Companies, Inc. China; 2011. p. 555.
6. Schellack G, editor. Pharmacology in clinical practice: application made easy for nurses and allied health professionals. 2nd ed. Claremont: Juta and Company, Ltd; 2010.
7. Smith H. Heartburn, gastro-oesophageal reflux disease and non-erosive reflux disease. Professional Nursing Today. 2019;23(3):13-16.
8. Chen J, Brady P. Gastroesophageal reflux disease: Pathophysiology, diagnosis, and treatment. Gastroenterol Nurs. 2019;42(1):20-28. https://doi.org/10.1097/SGA.0000000000000359.
9. DeVault KR, Castell DO. Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. Am J Gastroenterol. 2005;100(1):190-200. https://doi.org/10.1111/j.1572-0241.2005.41217.x.
10. Huerta-Iga F, Bielsa-Fernandez MV, Remes-Troche JM, et al.; on behalf of the 2015 GERD Study Group. Diagnosis and treatment of gastroesophageal reflux disease: recommendations of the Asociacion Mexicana de Gastroenterlogía. Rev Gastroenterol Mex. 2016;81(4):208-22. https://doi.org/10.1016/j.rgmx.2016.04.003.
11. Patti MG, Anand BS. Gastroesophageal reflux disease differential diagnosis. 2016. Available from: http://emedicine.medscape.com/article/176595-differential. Accessed 18 Jul 2022.
12. Brenner GM, Stevens CW. Pharmacology. 4th ed. China: Elsevier Saunders; 2013.
13. Holtmann G, Bigard MA, Malfertheiner P, Pounder R. Guidance on the use of over-the-counter proton pump inhibitors for the treatment of GERD. Int J Clin Pharm. 2011;33(3):493-500. https://doi.org/10.1007/s11096-011-9489-y.
14. Fong S, Dunn J. Dyspepsia: alarm symptoms, investigation and management. Prescriber. 2013;24:13-26. https://doi.org/10.1002/psb.1035.
15. Harmon C, Peura DA. E valuation and management of dyspepsia. Therap Adv Gastroenterol. 2010;3(2):87-98. https://doi.org/10.1177/1756283X09356590.
16. Tuskey A, Peura D. The use of H2 antagonists in treating and preventing NSAID-induced mucosal damage. Arthritis Res Ther. 2013;15(Suppl 3):S6. https://doi.org/10.1186/ar4178.
17. Mearin F, Calleja JL. Defining functional dyspepsia. Rev Esp Enferm Dig 2011;103(12):640-7. https://doi.org/10.4321/S1130-01082011001200006.
18. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Exp Rev Clin Pharmacol. 2013;6(4):443-51. https://doi.org/10.1586/17512433.2013.811206.
19. Ali RA, Egan LJ. Gastroesophageal reflux disease in pregnancy. Best Pract Res Clin Gastroenterol. 2007;21(5):793-806. https://doi.org/10.1016/j.bpg.2007.05.006.
20. Daily drug use. A guide for the health professional. 9th ed. South Africa: Tincture Press; 2010.
21. Amorim DC, Travassos MP, Dias IT, et al. Adverse reactions of proton pump inhibitors: A literature review. J Young Pharm. 2021;13(1):25. https://doi.org/10.5530/jyp.2021.13.5.
22. Schellack NS, Schellack GS, Meyer JM, et al. Gastro-oesophageal reflux disease: a pharmacist's perspective for 2020. S Afr Pharm J. 2020;87(3):31-37.