An approach to dyspepsia for the pharmacist

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Abstract

Dyspepsia is a symptom, or a combination of symptoms, that indicates the presence of an upper gastrointestinal tract problem. Typical symptoms include epigastric pain or burning, early satiation and postprandial fullness, belching, bloating, nausea or discomfort in the upper abdomen. Most people with dyspepsia do not seek medical care for their symptoms, although 25% of the developed world’s population suffers from dyspepsia annually. Rates range between 13-40% in different countries. Antacids remain safe, simple and effective agents for the symptomatic treatment of gastric acid-related symptoms. Evidence supports a test-and-treat approach in patients with non-dominant heartburn dyspepsia symptoms. In addition to antacids, dyspepsia is treated with proton-pump inhibitors (PPIs), H$_2$ blockers or cytoprotective agents, for example, sucralfate. Prokinetic drugs, for example metoclopramide, domperidone and erythromycin, also have a role to play in the treatment of dyspepsia. All patients should be offered general treatment, including advice on self-treatment, lifestyle changes, patient empowerment, and the management of long-term symptoms. Pharmacists are well placed to provide counselling and support to people suffering from dyspepsia.

Introduction

Stomach pain and discomfort have been reported since ancient times. The term “dyspepsia” originates from the Greek words dys and pepse, meaning indigestion.¹ It was first recorded in the mid-18th century, and since then, the term has been widely used. In the 18th century, dyspepsia was thought to be one of the “nervous disorders”, along with hypochondria and hysteria.¹

Dyspepsia is a sensation of pain or discomfort, centered in the upper abdomen.² It is often described as indigestion, early satiation (a sensation of having overeaten soon after beginning to eat, and out of proportion to the size of the meal, so that the food cannot be finished), postprandial fullness (prolonged persistence of food in the stomach), and gnawing or burning.² Dyspepsia is often accompanied by a combination of symptoms, including bloating, heartburn and nausea or vomiting. Enquiries should be made about predominant symptoms, such as upper abdominal discomfort, pain, heartburn or reflux, in order to distinguish dyspepsia from gastro-oesophageal reflux disease (GORD). Yet, symptom assessment alone cannot be used to make a reliable diagnosis in patients with dyspepsia.³

Symptoms

Symptoms are sometimes classified as ulcer-like, dysmotility-like, or reflux-like.² These symptoms suggest, but do not confirm, an aetiology, and often overlap:

- Ulcer-like symptoms consist of pain that is localised in the epigastrium, frequently occurs before meals, and is relieved by food, antacids or H$_2$ blockers.
- Dysmotility-like symptoms consist of discomfort, rather than pain, along with early satiation, postprandial fullness, nausea, vomiting, bloating, and symptoms that are worsened by food.
- Reflux-like symptoms consist of heartburn or acid regurgitation. Alternating constipation and diarrhoea with dyspepsia suggests irritable bowel syndrome (IBS), or abuse of over-the-counter (OTC) laxatives or antidiarrhoeals. The association between dyspepsia and IBS is a recurring theme in recent literature. Dyspepsia symptoms that cause alarm include anorexia, nausea, emesis, weight loss, anaemia, blood in the stools, dysphagia, odynophagia, and failure to respond to standard therapy, such as H$_2$ blockers.

Dyspepsia symptoms negatively affect the quality of life of most patients, especially with regard to sleep pattern changes, diet, and interference with work and leisure activities. The impact of dyspepsia upon quality of life is a personal experience. It can be a recurring problem, or a chronic complaint for which available treatment options may be wholly, or only partly, effective in relieving symptoms, while lifestyle changes can help to avoid trigger factors. It is appropriate to manage most patients’ symptoms (those without signs that cause alarm) without a formal diagnosis. Therefore, the pharmacist has an important role to play in counselling, monitoring and reassuring the patient with dyspepsia.
Epidemiology

Dyspepsia is one of the most common symptoms encountered in primary care. The exact prevalence of dyspepsia is unknown. Although most people who are affected by dyspepsia do not seek medical care for their symptoms, it is estimated that approximately one quarter of the population in the developed world suffers from dyspepsia annually, and nearly everyone, at some point in his or her life, will experience an episode of dyspepsia. Rates range from 13-40% in different countries. Dyspepsia remains a common and important symptom, even into the geriatric age group. Follow-up of patients over five to seven years shows a benign, but recurrent, nature in 50% of cases.

Terminology

The nomenclature for dyspepsia is confusing. Some people include all upper gastrointestinal tract symptoms under the heading of “dyspepsia,” while others separate patients with symptoms indicative of GORD. However, both approaches recommend identifying patients whose symptoms are suggestive of GORD, and managing them as if they have reflux disease.

“Dyspepsia” is pain or discomfort in the upper abdomen which is usually described as a burning sensation, heaviness, or an ache. Associated symptoms include a feeling of fullness, early satiation after meals, anorexia, bloating, belching, nausea and vomiting. The symptoms of dyspepsia may be episodic, recurrent, or chronic. Symptoms are often associated with eating, but this is not always the case.

“Undifferentiated or uninvestigated dyspepsia” is a condition for which characteristic symptoms have been clinically assessed as originating in the upper gastrointestinal tract, but which has not been investigated by upper gastrointestinal tract endoscopy recently. Symptoms include epigastric pain or burning, early satiety and postprandial fullness, belching, bloating, nausea, or discomfort in the upper abdomen. In a person at low risk of underlying pathology, symptomatic management is appropriate, without the need for further investigation. Accumulating evidence suggests that distinct subgroups of uninvestigated dyspepsia exist in the general population, signifying that separate evaluation and treatment strategies might be needed. Rome III introduced epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) subgroups to distinguish between different symptom clusters.

“Functional or non-ulcer dyspepsia” refers to a situation in which upper gastrointestinal tract endoscopy did not reveal a potential cause (underlying pathology) for the dyspepsia. In 1994, the Rome criteria were developed in an attempt to meet the clinical need to describe systematically functional gastrointestinal disorders. The Rome I criteria were subsequently modified in 2000 (Rome II criteria). The most recent 2006 Rome III criteria for functional dyspepsia are provided in Table I.

Functional dyspepsia includes multiple types of patients with heterogeneous complaints, and possibly different underlining pathophysiologies. Although the pathophysiology of functional dyspepsia has been widely investigated, no definite single reason was identified. Multiple mechanisms are likely to be involved (see Figure 1). Specific combinations of physiological, genetic, environmental and psychological factors in an individual patient lead to a variety of symptoms called dyspepsia. There is growing evidence that brain-gut interactions, at different levels, are also implicated.

Figure 1: Pathophysiological mechanisms in functional dyspepsia

[Diagram showing various mechanisms such as central nervous system modulation, stress, illness behaviour, visceral hypersensitivity, fat, H+ ions, wall distension, acid hypersensitivity, vagal neuropathy, delayed gastric emptying and antral hypomotility, duodenal hypersensitivity, inflammation, bacteria (Helicobacter pylori), viruses, decreased fundic accommodation, abnormal distribution of gastric contents, gastric dysrhythmias, overdistended antrum, small bowel dysmotility]
“Heartburn” is described as a burning sensation rising from the epigastrium, towards the neck. Heartburn is often included within the description of dyspepsia. Heartburn, with or without associated dyspepsia is most commonly associated with GORD or reflux oesophagitis. GORD and dyspepsia are related. Patients with troublesome heartburn and acid regurgitation can be diagnosed clinically as having GORD.

As already mentioned, the available literature increasingly states that IBS is often a co-morbid condition associated with dyspepsia. Therefore, there is a large overlap between GORD, IBS and dyspepsia, and they often co-exist in the same patient. For practical purposes, it is important to understand which complaints and symptoms are dominant. The severity of a patient’s dyspepsia is measured by the patient’s description of the impact of the symptoms on quality of life and function.

If different guidelines are compared, the Canadian Dyspepsia Working Group (CanDys) and the UK National Institute for Health and Clinical Excellence (NICE) include GORD symptoms in the definition of dyspepsia. CanDys does not require a specific duration of symptoms, whereas NICE requires four weeks, while the ROME III requires 12 weeks in the previous year to qualify as “dyspepsia”. The American Gastroenterological Association’s (AGA) technical review for the evaluation of dyspepsia excludes patients with symptoms that suggest GORD, and includes only the typical symptoms listed earlier.

**Aetiology**
Common causes of dyspepsia include peptic ulcer disease, motility disorders, medicines [for example, erythromycin, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), alendronate, angiotensin-converting enzyme (ACE) inhibitors, iron, macrolide antibiotics, metronidazole, oestrogen and theophylline], excessive alcohol, GORD, and oesophageal or gastric malignancy. Therefore, it is clear that the aetiology of dyspepsia differs, depending on which condition the patient is suffering from. In addition, many patients have no physical abnormalities (functional or non- ulcer dyspepsia). Others are found to have duodenitis, pyloric dysfunction, motility disturbances, *Helicobacter pylori*, gastritis, lactose deficiency, and cholelithiasis, which correlate poorly with the symptoms, i.e. correction of the condition does not alleviate dyspepsia.

**Examination and diagnosis**
Dyspepsia is not a diagnosis, but rather a description of intermittent symptoms that may indicate disease of the upper gastrointestinal tract. In the majority of cases, there is no clear pathological cause, and many people manage the symptoms themselves without consulting a healthcare practitioner. If medical advice is sought, a thorough medical and drug history should be undertaken by the healthcare practitioner to rule out serious pathology. When diagnosing dyspepsia, peptic ulceration (gastric or duodenal) is probably the most important diagnosis to rule out. Typically the patient will have well localised, mid-epigastric pain, described as constant, annoying or gnawing.

A physical examination rarely suggests a cause of dyspepsia.

**Testing**
Routine tests include a full blood count and stool testing for occult blood to exclude gastrointestinal blood loss. If results are abnormal, additional tests, for example imaging studies or endoscopy, should be considered.

Endoscopy is used to investigate signs that cause alarm, and to identify gastric and duodenal ulcers, as well as rare cases of oesophageal and gastric cancer. The important identification of the bacterium, *H. pylori*, in 1983, and the development of effective antibiotic treatment, has revolutionised treatment of peptic ulcer disease.

Because of malignancy risks, patients who are over 50 years old, and those with the onset of new symptoms that cause alarm, should undergo upper gastrointestinal tract endoscopy. For patients who are younger than 50 years without symptoms that cause alarm, empiric therapy with antisecretory or prokinetic agents, followed by endoscopy in treatment failures, has been suggested. Screening for *H. pylori* infection, with a urea breath test or stool assay, has also been recommended. Oesophageal manometry and pH studies are indicated if reflux symptoms persist after upper gastrointestinal tract endoscopy, as well as a two-to-four week trial using a proton-pump inhibitor (PPI).

**Questionnaires**
Several validated questionnaires have been developed, especially for functional dyspepsia. Examples are the Nepean Dyspepsia Index, Patient Assessment of Upper Gastrointestinal Symptoms (PAGI-SYM), and the Severity of Dyspepsia Assessment (SODA) questionnaire. These questionnaires do not differentiate between different types of dyspepsia patients according to symptoms or pathophysiology, and have mostly been used to define patients for the purpose of clinical studies.

**“Red flags” associated with dyspepsia**
When a patient presents, complaining of “indigestion”, healthcare practitioners should consider all possible sources thereof, including the oesophagus, stomach, heart, liver, gallbladder, pancreas, bowel, NSAIDs, and other medication.

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**Table I: Rome III diagnostic criteria for functional dyspepsia**

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<th>At least three months, with onset at least six months previously, of one or more of the following:</th>
<th>And</th>
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<tr>
<td>• Bothersome postprandial fullness</td>
<td>• There is no evidence of structural disease, including upper endoscopy, that is likely to explain the symptoms.</td>
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<tr>
<td>• Early satiation</td>
<td></td>
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<tr>
<td>• Epigastric pain</td>
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<td>• Epigastric burning</td>
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1. *EVIDENCE-BASED PHARMACY PRACTICE*
2. *S Afr Pharm J* 2012 Vol 79 No 8
The following factors increase the likelihood of significant organic disease, and are trigger points for referral:4,6

- Fifty years or older at first presentation (the incidence of gastric cancer increases with age)
- Family history of gastric cancer, with onset age younger than 50 years
- Severe or persistent dyspepsia
- Treatment failure
- Previous peptic ulcer disease, particularly if complicated
- Ingestion of NSAIDs, including aspirin
- Pain described as severe or debilitating, or wakes the patient at night
- Referred pain
- Signs and symptoms of chronic gastrointestinal tract bleeding, including dark or tarry stools
- Iron-deficiency anaemia
- Dysphagia, or the sensation that food is “sticking” in the throat
- Persistent or protracted vomiting with or without blood, or persistent regurgitation of food
- Palpable abdominal mass
- Coughing spells or nocturnal aspiration
- Unexplained weight loss
- Long-standing change in bowel habit.

Any of these “red flags” should be identified, and further investigated. They are major determinants of the need for endoscopy. The management strategy for uncomplicated dyspepsia should only be followed if there is reasonable certainty that no serious underlying pathology exists.

**Management strategy**

There are several options for initial management of the condition. Identifying a possible cause of the symptoms will guide management. Dyspepsia can be the result of medication or underlying pathology, including reflux oesophagitis, gastro-oesophageal cancer. However, the majority of patients have no distinguishable cause of their dyspepsia. These patients should be observed over time and reassured. The management goal is to provide relief of symptoms, and if present, to heal oesophageal lesions.

Direct clinical evidence supports a test-and-treat approach in patients with non-dominant heartburn dyspepsia symptoms.7 Symptoms are treated with PPIs,  \( \text{H}_2 \) blockers or cytoprotective agents, for example, sucralfate. Prokinetic drugs, for example, metoclopramide and erythromycin, given as a liquid suspension, may also be tried in patients with dysmotility-like dyspepsia. However, there is no clear evidence that matching the drug class to the specific symptoms makes a difference, for example, reflux vs. dysmotility. Misoprostol and anticholinergics are not effective in managing functional dyspepsia. Medicines that alter sensory perception, such as tricyclic antidepressants (TCAs), may be helpful.

Evidence shows that use of a PPI is superior to  \( \text{H}_2 \) receptor blockers in the initial treatment of  \( H. pylori \)-negative dyspepsia.7 Figure 2 illustrates an algorithm for the management of uninvestigated dyspepsia.

![Figure 2: Management of dyspepsia](image-url)
Conventional NSAIDs, aspirin and cyclo-oxygenase 2 inhibitors can all cause dyspepsia. If use of these medications cannot be discontinued, co-therapy with either a PPI, misoprostol or a high-dose H₂ receptor antagonist (blocker) is recommended, although evidence is based on ulcer data, and not on dyspepsia data. In patients with non-heartburn dominant dyspepsia, non-invasive testing for H. pylori should be performed, and if the result is positive, treatment must be given.

### Treatment

Various nonpharmacological measures and lifestyle changes can be recommended, for example, healthy eating habits, weight loss, and smoking cessation. Patients should be advised to avoid precipitating factors, such as coffee, chocolate, or fatty foods. Postural measures can be recommended, for example, the head of the bed can be raised, and the main meal eaten well before going to bed.

To treat dyspepsia, various complementary and alternative therapies have been investigated. Acupuncture has received considerable attention. Other treatments that have been evaluated include hypnotherapy, psychotherapy, herbal preparations derived from various plants containing complex extracts [for example, iberogast (herbal extract STW 5), Chinese and Japanese herbal medicine], and percutaneous implants of gastric electrodes.¹

From a pharmacological point of view, dyspepsia symptoms are managed by antacids, alginates, PPIs, H₂ receptor antagonists, H. pylori eradication therapy, prokinetics, TCAs and selective serotonin-reuptake inhibitors. Several other complementary and alternative treatments have been proposed.

Table II provides a summary of the most common treatments for dyspepsia, and evidence of their effectiveness.

### Antacids

For many decades, antacids have been used to treat dyspepsia, and have proven efficacy in neutralising stomach acid. Antacids act by neutralising gastric acidity; 5 ml of an average antacid liquid mixture should neutralise the normal fasting volume of gastric acid in the intact stomach.⁹ Generally, the doses required to relieve dyspeptic symptoms are not associated with unacceptable side-effects.⁹

Their neutralising capacity varies according to the metal salt used, as well as the onset and duration of action, for example:¹⁰

- Sodium and potassium salts are the most soluble, making them quick- but short-acting.
- Magnesium and aluminium salts are less soluble. Therefore, they have a slower onset, but longer duration of action.
- Calcium salts are both quick-acting, and have a prolonged action.

Antacid active ingredients are often combined in one product to ensure quick onset and prolonged action. The addition of local anaesthetics and anti-foaming agents (silicones as antiflatulants) adds no advantage to the efficacy of the antacid.⁹ The addition of an antispasmodic may appear to be advantageous in some patients, but separate treatment with an antispasmodic, if it is needed, is preferred.⁹

Antacids are easily available, and can be bought without the supervision of a pharmacist.

When recommending antacids, the following aspects should be considered:⁴

- Antacids in liquid form have a greater acid-neutralising capacity and speed of onset than tablet formulations.
- Misuse and chronic use of antacids will result in significant systemic absorption, leading to various unwanted medical conditions. Milk-alkali syndrome has been reported in connection with chronic abuse of calcium-containing antacids, and osteomalacia, in connection with aluminium-containing products. Therefore, prior to recommending a specific product, it is important to determine patient use of antacids. Preferably, antacid therapy should not be taken for longer than two weeks. If symptoms have not resolved within that time, then other treatments, or evaluation by a general practitioner, should be recommended.
- Antacids should be taken after food, because gastric emptying is delayed in the presence of food. This allows antacids to exert their effect for up to three hours.
- Avoid antacids that might cause constipation in the elderly.

### Alginates (alginic acid)

Alginates are extracted from algae. An alginic product should be the first-line treatment for patients with heartburn and reflux. When in contact with gastric acid, the alginic precipitates out,
forming a sponge-like matrix that floats on top of the stomach contents. Products containing alginate are combination preparations containing an alginate with antacids. They are best given after each main meal and before bedtime, although they can be taken when needed.

**H₂-receptor antagonists**

Ranitidine, famotidine and cimetidine are available in low dosages, without a prescription. Ranitidine can be given in a dose of 75 mg. If symptoms persist, another 75 mg dose may be given an hour later. The maximum dose of ranitidine is 300 mg in a 24-hour period. Famotidine can be given in a dose of 10 mg. If symptoms persist, another 10 mg can be administered an hour later. The maximum dose of famotidine is 20 mg in 24 hours.

**Proton-pump inhibitors**

The PPIs include omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole. These medicines are the most potent suppressors of gastric acid secretion. They act by irreversibly binding to, and inhibiting, H⁺/K⁺-ATPase enzyme of the gastric parietal cell. PPIs are indicated for the short-term management of peptic ulcer disease and GORD, the long-term prevention of GORD relapse, and as part of *H. pylori* eradication regimens. The available PPIs have comparable clinical efficacy.

**H. pylori eradication and other agents**

Evidence exists that eradicating *H. pylori* in non-ulcer dyspepsia is beneficial. Various other agents have been, or are, given, with varying success. Mucosal-protecting agents and antispasmodics are used, for example bismuth, sucralfate and misoprostol. Peppermint oil and caraway oil have been tried as spasmytic agents. The prokinetic agents, metoclopramide and domperidone, are offered. Tegaserod was withdrawn from the American market because of the increased incidence of cardiac ischaemic events. Itopride, which showed promising results in Phase 2 trials, ultimately failed in Phase 3 trials. Fundic relaxants have been given, as well as agents that have an effect on visceral hypersensitivity and central pain perception.

**Summary of medicines**

Table III provides a summary of selected medicines that are commonly used to manage dyspeptic symptoms.

**Conclusion**

Once an organic cause is excluded, dyspepsia remains a complex problem in clinical practice. Management of symptoms in primary care is appropriate for most patients, rather than routinely seeking a pathophysiological diagnosis. Many recent attempts to find new treatment strategies have failed. Tegaserod, for example, has been withdrawn from the United States, and itopride, which showed promising results in Phase 2 trials, ultimately failed in Phase 3.
trials. Future treatments will depend to a significant extent, on the careful evaluation of patients, and an analysis of their symptoms, as well as on new insights into the pathophysiology of symptoms in the upper gastrointestinal tract.

Pharmacists can provide both the first point of contact and ongoing support for patients suffering from dyspepsia. It has been demonstrated that advice on self-medication and counselling by pharmacists has a measurable impact on health-related quality of life, and that patients value the information that pharmacists provide. In managing dyspepsia, the role of the pharmacist is to offer initial and ongoing help for people suffering from symptoms, including advice about lifestyle changes, like, healthy eating, weight reduction and smoking cessation; over-the-counter and prescribed medicine; and when to consult a general practitioner. All patients should be given advice on self-treatment, lifestyle changes, and the management of long-term symptoms. Long-term care should emphasise patient empowerment in managing their condition.

References