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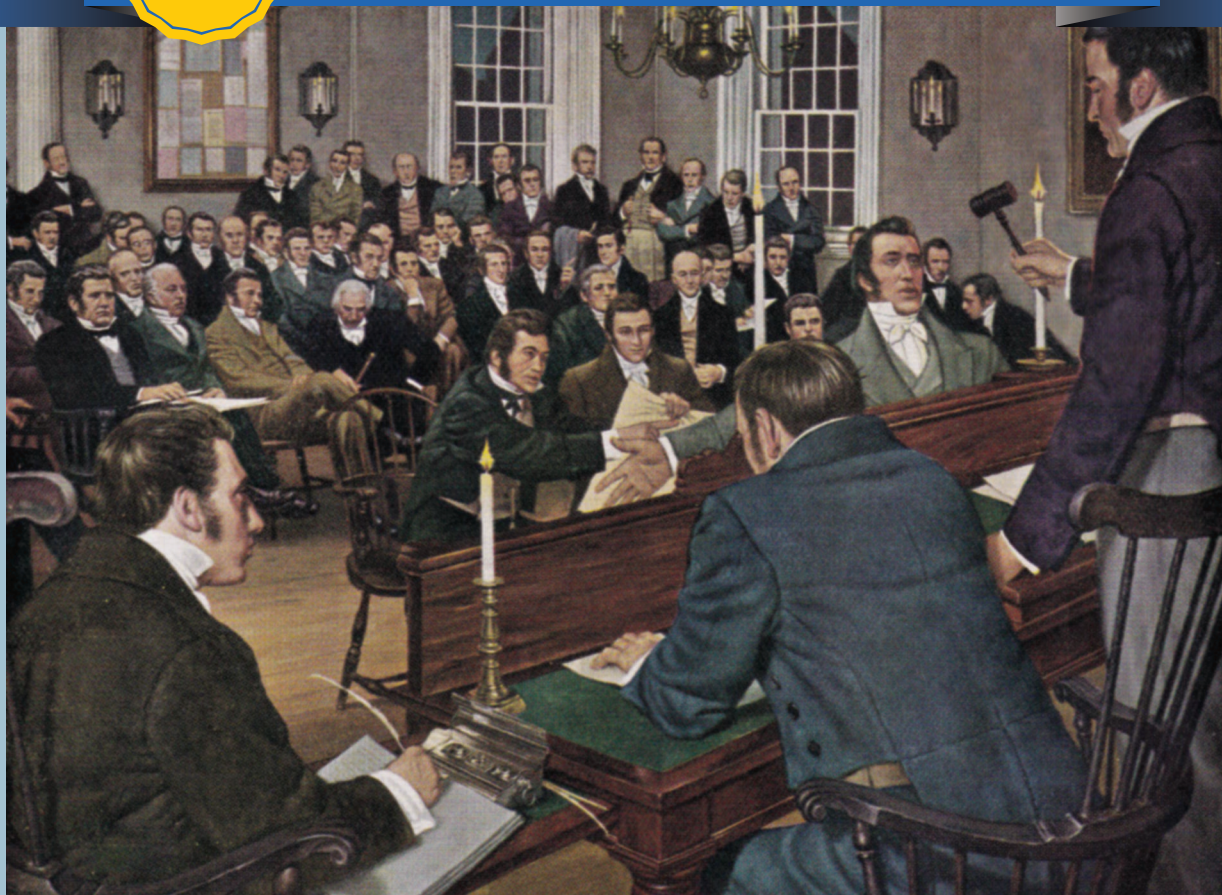
# The Sri Lanka Prescriber



March 2018; Volume 26, No. 1



**CELEBRATING THE 25<sup>TH</sup> ANNIVERSARY**



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# The Sri Lanka Prescriber

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## Cover picture

### AMERICAN PHARMACY BUILDS ITS FOUNDATIONS (1821)

The need for higher professional standards caused Philadelphia pharmacists to meet and form an association, and launch The Philadelphia College of Pharmacy, first American institution for pharmaceutical education.

One of a series: *A History of Pharmacy in Pictures*, presented by Parke, Davis & Company.

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## The Sri Lanka Prescriber celebrates 25 years of publication

The Sri Lanka Prescriber which celebrates 25 years of continuous publication in 2018, is Sri Lanka's only national independent drugs and therapeutics information bulletin. It is published quarterly by the Department of Pharmacology, Faculty of Medicine, University of Colombo and the State Pharmaceutical Corporation (SPC) of Sri Lanka. The primary purpose of the bulletin is to help health professionals in Sri Lanka make informed decisions when prescribing, by providing them with independent and reliable information about drugs and therapeutics.

The Sri Lanka Prescriber commenced publication in the present format in 1993 and 2018 marks the 25<sup>th</sup> year of continued publication. The Sri Lanka Prescriber evolved from the pocket size bulletin, 'The Prescriber' which began publishing in 1973 but went out of print in 1980's. Prior to that 'Formulary Notes', was in existence from 1966 which was the first drug information bulletin published in Sri Lanka. Formulary Notes was also a pocket size bulletin, published on behalf of the Formulary Committee, initiated by Professor Senaka Bibile, the first Professor of Pharmacology, University of Ceylon and the Editor of Formulary Notes, to provide unbiased drug information to healthcare professionals. As the Formulary Notes had difficulties in publication, 'The Prescriber' was launched in 1973 as a joint publication between the Formulary Committee and the State Pharmaceuticals Corporation (SPC), with funding and distribution managed by the SPC. The Sri Lanka Prescriber commenced as a joint publication by the Department of Pharmacology, Faculty of Medicine, University of Colombo and the SPC in 1993.

The Sri Lanka Prescriber became a full-member of the International Society of Drug Bulletins (ISDB) since 2001. In accordance with ISDB policy the Sri Lanka Prescriber does not accept advertising and/or other forms of sponsorship. This enables the bulletin to be wholly independent of the industry and other regulatory authorities, allowing it to publish freely and impartially on all matters related to medicines. Although the SPC bears the publication costs it does not play any role in the contents of the bulletin.

The print copy of The Sri Lanka Prescriber has a circulation of 7000, distributed free of charge to Sri Lankan healthcare professionals, including prescribing doctors, academics, researchers and students in universities, not only in medicine and dentistry but also in pharmacy. The bulletin has been made available online via websites of the SPC and the Department of Pharmacology Colombo since 2007.

For well over two decades, the bulletin has provided accurate, independent evaluations and practical advice on drugs and therapeutics for doctors, pharmacists and other healthcare professionals. The Editorial Board of the Sri Lanka Prescriber consists of experts from a variety of disciplines, including pharmacology, clinical medicine, paediatrics, gynaecology and obstetrics, psychiatry, anaesthesiology and dentistry. Surveys of our readership have consistently shown that readers find the bulletin influential in relation to their decisions, recommendations or advice on treatments, becoming an indispensable part of evidence based clinical practice in Sri Lanka. The Sri Lanka Prescriber is funded by the State Pharmaceuticals Corporation (SPC) of Sri Lanka as a service to the medical profession.

**Editorial Board, The Sri Lanka Prescriber**

# Benign prostatic hyperplasia

## Introduction

Benign prostatic hyperplasia (BPH) is proliferation of prostatic stromal cells leading to enlargement of the gland. As it is a pathological diagnosis, the term benign prostatic enlargement is clinically more appropriate. In some men with BPH the prostatic urethra is compressed, restricting the flow of urine. This may cause a symptom complex known as lower urinary tract symptoms (Panel 1). BPH is present in about 50% of men above 60 years. With increasing awareness about men's health in the society and concerns about prostate cancer, more men are seeking medical help for lower urinary tract symptoms (LUTS). Availability now of effective oral medications persuade more men to seek treatment than in the past.

### Panel 1. Lower urinary tract symptoms

Voiding symptoms	Storage symptoms
Slow stream	Frequency
Thin stream	Nocturia
Hesitancy	Urgency
Sense of incomplete emptying	Urge incontinence
Terminal dribbling	Nocturnal enuresis
Post-micturition dribbling	

## Pathophysiology

Bladder outflow obstruction from BPH is caused by increased size of the gland as well as by increased tone of the smooth muscle component of the stroma of the gland. The main mediator of prostatic growth is dihydrotestosterone. It is a metabolite of testosterone and is formed inside the prostatic glandular cells by the action of enzyme 5-alpha reductase. 5-alpha reductase inhibitors used in the treatment of BPH targets this enzyme. BPH is not a precursor or a risk factor for prostate cancer.

## Clinical features

LUTS can be divided into voiding and storage symptoms. Voiding symptoms respond better to treatment (both medical and surgical) than storage symptoms. The severity of symptoms does not relate to the size of the prostate gland in a linear fashion. If the gland enlarges peripherally, the urethra may not get compressed. On the other hand, even a small gland can cause severe symptoms if it enlarges towards the bladder neck. About 30% of men with LUTS, especially its storage symptoms, have concurrent overactive bladder due to detrusor muscle overactivity. They will require treatment additionally for overactive bladder

for effective symptom relief. International Prostatic Symptom Score (IPSS) based on a questionnaire filled by the patient is used to assess the severity of symptoms objectively. This helps to compare the efficacy of treatment during follow-up, too.

Those who do not seek treatment for LUTS at an early stage may develop acute urinary retention, chronic urinary retention, recurrent urinary infections or bladder calculi. Some men with chronic retention of urine have clinical features of chronic renal impairment consequent to upper urinary tract dilation. Characteristically they tend to have recent onset nocturnal enuresis and a non-tender palpable bladder. A small number of patients with BPH especially those with very large prostate glands and taking anti-platelet drugs develops haematuria. However, more sinister causes such as cancer of the urinary tract (kidney, ureter, bladder, prostate, urethra) should be excluded before the haematuria is attributed to BPH.

Clinical evaluation of patients with LUTS and bladder outlet obstruction (BOO) should attempt to exclude other possible causes like prostate carcinoma, phimosis, urethral meatal stenosis, urethral stricture disease and neurological problems like parkinsonism, multiple sclerosis, spinal cord lesions and stroke.

## Investigations

Urinary tract ultrasonography is useful to assess residual urine volume, size of the gland, especially the length of its intravesical protrusion, upper tract status, bladder wall thickness and bladder calculi. Residual urine volume changes with age, and some elderly men with raised residual volumes may not require treatment. Large prostate glands respond better to 5-alpha reductase inhibitors and those with large intravesical protrusions respond poorly to pharmaceutical agents. Those with chronic retention of urine and upper tract dilation require surgical treatment rather than pharmaceutical agents. Interpretation of bladder wall thickness is difficult as it depends on the volume of the bladder and area of the wall assessed. Routine ultrasonography in patients with BOO may find incidental pathologies such as renal masses, hepatobiliary and pancreatic pathology.

If renal impairment is suspected, serum creatinine and E/GFR measurement is indicated. If there is clinical evidence of a urine infection a midstream specimen of urine should be sent for culture and ABST. If the patient's account of urinary stream cannot be relied upon and the clinician needs documentation of objective evidence, uroflowmetry can be done. A urine flow rate less than 10 ml/s (for a voided urine volume more than 150 ml)

indicates BOO in men though the cut-point value could vary with age. Flexible cystourethroscopy is not indicated in patients with BOO due to BPH although it is done by practitioners frequently for monitory reasons.

Measurement of serum prostate specific antigen (PSA) as a tumour marker for prostate cancer in patients with BOO due to BPH is debatable and should be offered with caution and after appropriate counselling. If digital rectal examination shows a clinically benign prostate and if the age is less than 70 years a serum PSA test after explaining to the patient about pros and cons of the test (Panel 2) may be useful to identify a prostate neoplasm as part of opportunistic screening. However, taking into consideration that average life expectancy of a Sri Lankan man is 72 years, serum PSA is unlikely to be useful in prolonging life in a man who is more than 70 years old and has a clinically benign prostate. Acute urinary retention, urethral catheterisation and urinary tract infection are known to raise the serum PSA level in the absence of a prostatic malignancy. If a decision is made to measure the serum PSA level, it is sensible to do the test 3 weeks after the acute event to avoid false positives. Recently PSA has been found to be useful as a marker of prostate size and BPH progression in the absence of a malignancy. If the PSA is more than 1.5 ng/ml such patients are more likely to respond to 5-alpha reductase inhibitors.

## Treatment

### *Lifestyle changes*

Treatment of BPH should be individualised. Many patients with mild symptoms with especially storage symptoms would benefit from lifestyle modifications which may be the only form of treatment required. These include decreasing alcohol and caffeine consumption, restricting fluids before bedtime to improve nocturia and timed voiding. Some patients believe that it is necessary to drink lot of liquids even at night to avoid kidney disease, and this results in disabling nocturia. Such patients should be reassured and correct advice given. Men may seek advice for an enlarged prostate gland noted as an incidental finding in abdominal ultrasonography. If asymptomatic and a cancer is excluded they do not need any form of treatment. That prostatectomy would prevent the occurrence of a cancer in the future is a myth. Surprisingly, many medical personnel believe this to be true! During transurethral resection of the prostate (TURP) only the enlarged adenomatous component of the gland is removed, and the chance of getting a cancer is unaltered. Some elderly patients with mild symptoms of BPH seek medical advice mainly for fear of a prostate malignancy. They may have experienced the recent bereavement of a friend, relative or a contemporary from prostate cancer. It is important to identify such fears and reassure them.

### **Panel 2. Patient information leaflet**

#### **Blood PSA test**

Doing the PSA test, in the absence of suspicious symptoms or examination findings (clinical features) has both advantages and disadvantages, and some of them may be serious. Therefore, please study and understand the benefits and risks before you decide to have the test.

#### **Benefits**

1. It may provide reassurance if the test result is negative.
2. It may find cancer before symptoms develop.
3. It may detect cancer at an early stage when treatment could be beneficial.
4. If treatment is successful, the consequences of more advanced cancer (eg bone fractures, paralysis of lower limbs) are avoided.
5. It may reduce your chances of dying of prostate cancer.

#### **Downsides**

1. It can miss cancer and provides false reassurance (even with normal PSA result cancer may be present).
2. It may lead to unnecessary anxiety and medical tests when no cancer is present. Those tests can be costly and may cause serious complications like severe infections, bleeding and urine block.
3. It might detect slow growing cancer that may never cause any symptoms or shorten your life.
4. The main treatments of early prostate cancer have significant side-effects (continuous urine leakage, erectile dysfunction, bleeding from urinary passage and bowel) and there is no certainty that the treatment will be successful and prolong your life.
5. Cost of the test.

### Herbal medicine

Plant extracts (phytotherapy) are widely used by patients all over the world for the treatment of BPH. Some of these compounds (saw palmetto – *Serenoa repens*, African plum – *Pygeum africanum* and *Corni Fructus*) have improved symptoms in small studies, but recent robust analyses have failed to show any advantage. Different plant extracts are used by patients in Sri Lanka too, though those agents have not been evaluated in rigorous studies. A large number of patients use these at least for a short period. It is possible that certain subgroups of patients yet unidentified may benefit from these agents.

### Pharmacological treatment

Two main classes of therapeutic agents used to treat BPH are alpha blockers and 5-alpha reductase inhibitors (5-ARIs). Recently another third group has been added – phosphodiesterase inhibitors.

Alpha-blockers reduce the tone of smooth muscle of the prostate and bladder neck by blocking the alpha-1a receptors. The alpha-blockers have a quick onset of action, within 3-5 days. Prazosin, terazosin, alfuzosin, tamsulosin and silodosin are the commonly available alpha-blockers. All five agents are more or less equally effective though their side-effects profiles are different (Panel 3). Prazosin and terazosin may cause hypotension, hence require dose titration. Tamsulosin, alfuzosin and silodosin have fewer cardiovascular side-effects and do not require dose titration. Retrograde ejaculation is a worrying adverse effect in about 10% of patients using the latter drugs. It is interesting to note that those who developed retrograde ejaculation had the urine flow rates improved most. Intraoperative floppy iris syndrome has been reported with alpha-blockers and ophthalmologists should be informed of such drugs if the patient is to undergo cataract surgery. Although prazosin has a poor side-effects profile compared to others, it is a widely used drug in resource limited settings due to its low cost and availability. Silodosin is a super-selective alpha-blocker as it blocks alpha-1a receptors mainly with little effect on alpha-1b and alpha-1d receptors. This heightened selectivity results in minimal cardiovascular side-effects.

The 5-ARIs (finasteride and dutasteride) inhibit the

conversion of testosterone to dihydrotestosterone, the main mediator of BPH development. This leads to decrease in the size of prostate. The onset of action is slower and reaches full therapeutic potential only after 6 months. Finasteride inhibits the type 2, 5-alpha reductase isoenzyme, while dutasteride inhibits both type 1 and type 2 isoenzymes. Hence, dutasteride lowers dihydrotestosterone production by 90% whereas finasteride lowers by 70%. This may result in faster onset of action with dutasteride compared to finasteride.

Alpha-blockers do not affect serum PSA level and do not alter prostate cancer risk. In contrast 5-ARIs lower PSA by about 50% after 6 months of treatment. This should be taken into consideration when these patients are followed up and reassessed for the possibility of developing a prostate cancer using rising PSA levels. Controversy still exists about the increased risk of developing high grade prostate cancer in patients taking 5-ARIs despite two major trials showing no significant risk.

Combination of both alpha-blockers and 5-ARIs has been shown to be beneficial with patients with large prostates. 5-ARIs are effective in prostate glands larger than 30-40g and this can be ascertained clinically, ultrasonographically and by serum PSA level. Combination therapy increases the flow rate, improves symptom score, reduces risk of urinary retention and reduces need for future surgery. For patients with smaller prostates alpha-blockers alone may be sufficient.

Phosphodiesterase-5 (PDE-5) promotes smooth muscle contraction; hence PDE-5 inhibitors may have a role in smooth muscle relaxation in BPH. Studies have shown improvements of LUTS in patients with BPH who are given oral PDE-5 inhibitors. The agents used are sildenafil, tadalafil and verdanafil.

### Surgery

Patients who are started on pharmaceutical agents should be reassessed in 1-3 months. Response to medical treatment can be assessed clinically by symptomatic improvement. This can be confirmed by an ultrasonographic assessment of the residual urine volume in the bladder and by uroflowmetry.

### Panel 3. Pharmaceutical agents used in treatment for BPH

Name	Dose	Adverse effects
Prazosin	0.5 mg daily to 1 mg tid	First dose syncope, dizziness, hypotension, headache, asthenia
Terazosin	1 mg to 5 mg daily	Same as above
Tamsulosin	0.4 mg to 0.8 mg daily	Ejaculatory dysfunction, rhinitis, floppy iris syndrome
Silodosin	4 mg to 8 mg daily	Minimal retrograde ejaculation
Finasteride	5 mg daily	Decreased libido, gynaecomastia
Dutasteride	0.5 mg daily	Decreased libido, gynaecomastia



If there is poor response to drugs or poor compliance because of side-effects or cost, surgical options should be considered. Those who develop acute urinary retention should have a trial of catheter removal after 5-7 days of alpha-blocker therapy. If the trial fails they should be offered surgery. The most common surgical procedure for BPH is TURP. Post-operative haemorrhage is the troublesome complication of TURP. The other complications include sepsis, TURP syndrome, cardiac events, urinary incontinence and stricture formation. Retrograde ejaculation and erectile dysfunction are the possible sexual side effects. Several energy sources have been described for resection of tissue during TURP. TURIS and laser prostatectomy are claimed to have less post-operative complications, especially in patients with high cardiac and bleeding risk. Prostatic urethral lift is the most recent minimally invasive procedure that is being promoted and evaluated. Despite introduction of new alternatives, traditional TURP remains the gold standard worldwide due to its efficacy, safety and low cost in experienced hands.

Patients with chronic retention of urine respond poorly to drug therapy and should be offered early prostatic surgery. If there is associated renal impairment it is advisable to decompress the bladder by an indwelling catheter for a few weeks before surgery. Decompression of the bladder may cause post-obstructive diuresis (which may lead to hypotension, hyponatraemia and hypokalemia), and bleeding in the form of haematuria. Hence this should be

done under supervision, especially in elderly patients. Rarely, BPH may cause episodes of haematuria which can be severe. Treatment with 5-ARIs may be useful in these patients. If this is unsuccessful, TURP may be indicated.

### Suggested reading

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## Self Assessment MCQs

(Any number of items in each MCQ may be true or false)

### 1. Irritable bowel syndrome is associated with

- (a) gastrointestinal malignancies
- (b) a positive test for faecal occult blood
- (c) weight loss
- (d) abdominal pain related to defecation
- (e) a change in frequency or form (appearance) of stool

### 2. Tamsulosin

- (a) is an alpha-1 receptor blocker
- (b) reduces prostate volume in long-term use
- (c) is known to produce postural hypotension in patients receiving anti-hypertensive medication
- (d) is known to produce floppy iris syndrome during cataract surgery
- (e) increases urine flow rate and improves obstructive symptoms in BPH

### 3. Regarding phosphodiesterase inhibitors

- (a) type-5 are of proven efficacy in erectile dysfunction
- (b) type-3 increase survival in heart failure
- (c) type-4 are indicated as an adjunct to bronchodilators in COPD
- (d) type-5 are known to cause anterior ischaemic optic atrophy

Answers on page 10

# Medication safety: current status and guidance for practice

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Medication safety has become a topic of current interest with several reports showing that medication errors account for a large number of preventable deaths in several countries in the world. In the USA about 7000 people are estimated to die annually due to medication errors [1]. In the UK medication errors annually account for 712 deaths and contribute to another 1,708 deaths according to a 2018 report [2]. Furthermore, medical error was identified as the third leading cause of death in the USA, after heart disease and cancer in 2016 [3]. A medical error may or may not be related to medicines given to the patient. It is estimated that there are 180 000 iatrogenic deaths per year in the USA and 51%-78% of those are considered preventable [3,4].

In developed countries, 3-16% of patients and on average about one in 10 patients are harmed while receiving hospital care [5]. According to the World Health Organisation (WHO) and World Alliance for Patient Safety, aviation and nuclear power plants have much better safety records as risk of death during air travel is estimated to be 1 in a million, while risk of death due to medical errors is estimated at 1 in 300.

Considering these figures, WHO launched a global patient safety challenge on medication safety in 2017 with an overall goal of reducing medication errors by 50% in the next 5 years. Each country is requested to take steps to prevent medication errors to contribute to global reduction of medication errors.

## Medical error vs medication error

A medical error could be related to a medicine used to treat a patient, when it is termed a medication error and is defined as “a failure in the treatment process that leads to, or has the potential to lead to harm the patient” [6, 7]. Data on medication errors from developed countries show that about 5-20% patients admitted to hospitals experienced adverse drug events (ADE) and 20-50% of these were considered preventable (8-9). Worldwide, the cost associated with medication errors has been estimated as \$42 billion annually.

Statistics on medication errors in low and middle-income countries are limited so the true burden of unsafe medication practices is considered underestimated. Systematic review of medication error from South-east Asia, have described the types and causes of medication errors noted in the region [10].

## Causes of medication errors

Medication errors could occur at various stages in medication use (Panel 1). Some reported examples of errors noted at different stages of medication process and the reasons for the occurrence of these errors are given in Panel 2.

The relative frequency of the errors occurring at different stages varies widely. In a study from UK, medication errors reported showed that errors occurred at every stage of the medication treatment process with 16% in prescribing, 18% in dispensing and 50% in administration of drugs [11]. In a systematic review from the Middle East, error rates varied from 7.1% to 90.5% for prescribing, and from 9.4% to 80% for administration [12]. The most common types of prescribing errors reported were incorrect dose, wrong frequency and wrong strength.

In the UK over a 5-year period, 221 deaths and 551 serious errors occurred due to medication incidents [11]. Most common errors reported in UK were omitted or delayed medicine use (15%), wrong dose (15%), wrong medicine (9%), wrong frequency (8%), wrong quantity (5%) and mismatch between patient and drug (4%).

## Medication errors reported in Sri Lanka

Data on medication errors from Sri Lanka are limited. A prescription survey from two areas (Aluthgama and Kandy) in Sri Lanka reported poor legibility in 50% of prescriptions and use of non-standard abbreviations in 37% [13]. Another study on 1000 prescriptions dispensed from the private sector in North Central Province reported legibility in only 26%, and most prescriptions were

### Panel 1. Stages in medication when errors occur

- **Prescribing** – when the prescription is written
- **Transcribing** – when the prescribed medicine is written into drug chart/labels
- **Supplying/dispensing** – when the prescribed medicine is supplied to the patient
- **Preparing** – when the medicine is prepared for administration to the patient
- **Administering** – when the medicine is given to the patient.
- **Monitoring treatment** – during clinical or laboratory monitoring while the drug is administered

legible only with effort (65%), and illegibility in 9% of prescriptions [14]. This study reported presence of potential drug interaction in 53% prescriptions. Incomplete, absence or incorrect details on route, dose, frequency and duration was found in 94%, 70%, 34% and 23% prescriptions respectively. Error prone abbreviation use was 69% in a study reported from Sri Lanka [15].

Another study analysed details of 503 prescription errors recorded by trainee internal pharmacists in their portfolios [16]. The most common errors were in the dose (42%), drug name (32%) and frequency of administration (28%). The probability of the error reaching the patient was considered as high in 18% and the severity of harm was considered as severe in 17 instances.

### **Factors responsible for medication errors and actions for prevention**

#### **Medication factors**

Some medications, which are look or sound similar, are easily confused. These LASA medicines (Panel 3) contribute to medication errors. Different preparations or dosages of similar medication may have similar names or packaging. Small prints in labels may be so difficult to read, contributing to errors. Writing some letters in capitals

(Tall man lettering) to prevent errors by avoiding confusion with another similar sounding drugs can be used to prevent errors due to LASA medicines (Panel 3). Avoiding storage of LASA medicines near each other could prevent errors.

Some medicines have been commonly reported to cause more errors and harm than others, and these are identified as high-risk or high alert medicines. These are more likely to cause errors or they bear a heightened risk of causing significant patient harm when used in error (Panel 4). Although mistakes may not be more common with these drugs, the consequences of an error are more likely to cause serious harm and death (eg, muscle relaxants, intravenous potassium preparations). Health care professionals have to pay extra care when prescribing, dispensing or administering these medicines. Double-checking is important with such medications.

#### **Staff factors**

Inexperienced personnel such as intern house officers, pharmacists and nurses are more liable to make errors. Studies have shown an increase in mortality rates due to medication errors in the month of new interns starting to work in UK [17]. Factors such as rushing in emergency situations, multitasking, getting interrupted mid-task

## **Panel 2. Examples of reported medication errors that occurred at different stages**

### **Prescribing errors**

- A 6 year-old child weighing 20 kg was prescribed paracetamol 1 tablet (500 mg) 3 times/day and the child was admitted to hospital with liver damage. Correct dose at 10-15 mg/kg is maximum of 300 mg per dose and nearly double the dose was administered, **due to incorrect calculation of dose**
- Patient prescribed calcium tablets was written as CaCO<sub>3</sub> and was dispensed lithium carbonate. Patient was admitted with lithium toxicity and renal failure requiring dialysis. Pharmacist thought it was lithium carbonate written as LiCO<sub>3</sub> **due to error prone abbreviation used**

### **Dispensing errors**

- Patient with asthma was prescribed prednisolone 30mg (6 tablets of 5 mg) but was dispensed Glibenclamide 30 mg (6 tablets of 5 mg). Patient became unconscious with hypoglycaemia and survived with brain damage. Both prednisolone and glibenclamide were white colored small tablets and pharmacist mistook glibenclamide due to **'Look Alike Sound Alike' (LASA) medicines**
- Propranolol 40 mg was dispensed for prednisolone 40 mg for a patient with asthma, and patient became breathless, hypotensive with coma and died. Both drugs were written alike and packaging and labelling of medicines also looked the same. Error occurred due to **LASA medicines**
- Patient prescribed metformin 500mg bd was dispensed methotrexate 5 mg bd and patient developed agranulocytosis and died. This was also due to **LASA medicines**

### **Administration errors**

- A child prescribed ampicillin IV was given aminophylline IV. The error was identified only when child developed fits and cause was looked for. Child ended with brain damage. The drugs were **LASA medicines and illegibility of prescription** contributed to the error
- A patient prescribed 6 U insulin was administered 60 U insulin and developed severe hypoglycaemia. Unclear dose due to using **an error prone abbreviation** contributed to the error



### Panel 3. Look alike and sound alike (LASA) medicines that have caused errors

#### Sound alike (SA) medicines with examples of Tall man lettering used to prevent errors

- CarbamaZEPine and CarbemaZOLe
- ClonaZEPam and cloZAPine
- PrednoSOLne and proPRAnolol
- MetFORmin and methoTReXate
- Phenytoin (Dilantin) Sodium and Diclofenac sodium (often written as D sodium)
- Liposomal amphotericin B and liophylised amphotericin B
- FlunnaRAZine and FluoXETine
- OmePRAZole and OlaNZAPine
- TheoPHYLLine and ThyROXine
- AmioaDARone and AmLODipine
- DiGOXine and ThYROXine
- ClonaZEPam and OlanZAPine
- AtorVASTatin and AmiTRIPTYline

#### Look alike (LA) medicines

- Prednisolone and glibenclamide (both white coloured small tablets)
- Propranolol and salbutamol (both pink coloured small tablets)

### Panel 4. High risk medicines that are known to cause serious medication errors

#### Drug classes

Opioids - morphine, oxycodone  
Insulins  
Anticoagulants  
Antipsychotics  
Anti-infectives – penicillins, cephalosporins, vancomycin, amphotericin B,  
Benzodiazepines  
Non Steroidal Anti Inflammatory Drugs  
Electrolyte solutions – potassium  
Muscle relaxants  
Immunosuppressants  
Chemotherapeutic agents  
Central nervous system depressants

#### Individual drugs

Potassium  
Adrenaline  
Phenytoin  
Amioadarone  
Methotrexate  
Vincristine  
Lithium  
Clozapine  
Midazolam  
Paracetamol  
Penicillins, cephalosporins  
Gentamicin, tobramycin

(eg. during prescribing or drug administration), fatigue, and lack of vigilance also contribute to errors. Lack of checking and double-checking habits of staff promote medication errors. Health care professional should ensure the '5 rights' when writing a prescription, or dispensing or administering a medicine (Panel 5). As studies have shown a high prevalence of poor handwriting, which has a high risk of leading to errors, every effort should be taken to

write prescriptions legibly. The use of error prone abbreviations (Panel 6) is another cause for errors and these should be avoided. Introducing the WHO medication safety curriculum into undergraduate and postgraduate teaching of health care professionals will improve the knowledge and training on medication safety. Other methods that health care professionals can adopt to prevent medication errors are given in Panel 7.

### Panel 5. Some error prone abbreviations to avoid

Abbreviation or writing to be avoided	Preferred method of writing
d	daily or days
µg	microgramme
u	units
n	night or nocte
m	mane or morning
OD	once daily
.5 mg	0.5 mg (put a 0 in front as mistaken for 5 mg)
5.0 mg	5 mg (avoid trailing 0 as mistaken for 50 mg)
D. Sodium	Diclofenac sodium
CaCO <sub>3</sub>	Calcium Carbonate

### Panel 6. The '5R's in preventing medication errors

- Right drug
- Right dose
- Right route
- Right time
- Right patient

### Panel 7. Some ways for health care professionals to make medication use safer

- Use generic names
- Tailor prescribing to individual patients
- Learn and practice collecting complete medication histories
- Medication histories to be taken by both doctors and pharmacists.
- Know the high risk medicines and be cautious when prescribing them
- Be thorough with the commonly prescribed medications
- Use memory aids eg. BNF, eBNF/Medscape often
- Check on 5Rs when prescribing, dispensing or administering medication
- Communicate clearly
- Develop checking habits
- Report and learn from medication events

### Patient factors

Poor knowledge of patients on medicines they take is one of the most important factors responsible for errors. A significant number of patients taking long-term medicines do not know the names of medicines or doses they use. Most patients identify medicines from the shape or colour and the dose in the number of tablets rather than in units. Some patients with specific conditions are more vulnerable and prone to errors (e.g. patients on multiple medications, having several diseases or those with organ dysfunction). Informing patients about the medicines prescribed is a responsibility of prescribers. Improving medication literacy, i.e. the knowledge of patients on medications prescribed to them is important to prevent errors. The minimum information that should be provided to patients include the names of the prescribed medicines, the indications for each drug prescribed, the dose of each drug to be taken, frequency of use and any special advice on taking or on monitoring required.

### Workplace design

Absence of a safety culture in the workplace, lack of reporting systems, failure to learn from past near misses and adverse events, inadequate or untrained staffing contribute to increase medical errors. In Sri Lanka there are no clinical pharmacists in wards to review drugs prescribed for patients. In developed countries, clinical pharmacists working in the wards play an important role in reducing medication errors. Inappropriate storage of medications is another factor contributing to errors. Electronic prescribing should reduce errors due to illegible handwriting. Implementing a medication incident reporting system could identify causes of serious errors in the local setting to take preventive actions. Establishment of health care quality and safety units in Sri Lankan hospitals is expected to promote reporting of adverse events in a blame free culture, which would facilitate preventive actions.

### Special situations for errors and actions for prevention

#### Polypharmacy

Polypharmacy refers to use of multiple medications for a single patient, generally considered when 5 or more drugs are prescribed, makes patients more prone to errors. However a patient with multiple conditions such as diabetes, hypertension and heart disease may be in need of several drugs for each condition. Prescribing more drugs than the patient needs, for the diagnoses, without considering side-effects, indicates inappropriate polypharmacy. Minimising the use of medications that are ineffective or non-essential could avoid non adherence to essential medications. As patients are unaware of the indications for each drug, they may not take essential medications while taking non-essential vitamins and other symptomatic medications. Simplifying medication regimens is particularly helpful.

### **Transitions of care**

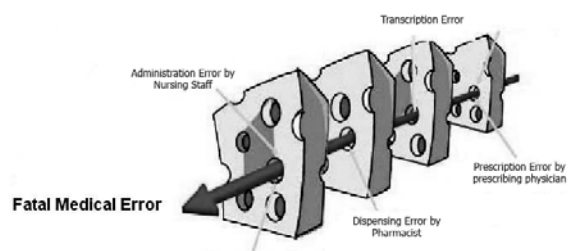
When patients transfer from one setting to another, such as during hospital admission or discharge, medication errors could occur. During hospital admissions the usual medicines patients take may not be correctly recorded, and during discharge any changes to medication may not be accurately recorded. These could result in serious harm if long term medications such as antihypertensives, antidiabetics, anticoagulants, antiepileptics etc., are not continued. These medication errors could also occur during any interaction with a health care professional even at an out-patient visit. Medication reconciliation, i.e. careful check on the accuracy of medicines the patient needs to take, at these points of transition has been shown to prevent medication errors. Clinical Pharmacists in the wards often attend to medication reconciliation in other countries and in the absence of this service in Sri Lanka, doctors need to attend to medication reconciliation and take extra care to avoid medication errors during transitions.

### **High risk situations**

Certain situations such as emergencies, intensive care, anesthesia, multi-morbidity are other instances when medication errors could occur with serious consequences. Having adequate number of trained staff, careful checking and training of staff can prevent errors occurring in these situations.

### **Other aspects of prevention of medication errors**

Medication errors can be prevented at each stage (Panel 1) of medication use process before progressing to next stage. However only 26% of medication errors were detected before advancing to subsequent stage. Errors reaching the patient are not due to the inappropriate actions of one person but due to a combination of factors that result in a system failure. A model known as the Swiss cheese model (Figure) where holes in the cheese represent lapses at each stage of medication process that can result in errors is used to describe how these barriers can be used effectively to prevent errors [16]. Some recommendations to minimize medication errors in Sri Lanka are given (Panel 8).



Picture : Swiss - Cheese Model

**Figure. Swiss cheese model for preventing medication errors**

### **Panel 8. Recommendations to ensure medication safety in Sri Lanka**

- Establish a medication incidents reporting system for hospitals and private sector
- Encourage reporting by both health professionals and patients
- Promote a no blame culture to encourage reporting
- Learn from mistakes and taking action for prevention
- Improve medication literacy of patients
- Introduce the necessity to know about medicines taken by patients into school curricula
- Introduce WHO medication safety curriculum into undergraduate and postgraduate teaching
- Emphasise the need for legible prescribing by doctors
- Limit the number of generics registered unless there is a necessity
- Identify and prevent registration of medicines prone for errors, by requesting labelling and other necessary changes at the time of registration by NMRA
- Pharmacists/nurses/doctors to take steps to prevent errors due to look alike sound alike and medicines and high risk medicines when these are identified or reported
- Ensure dispensing medicines with labels on drug names and instructions mandatory
- Continuing professional development activities for doctors, nurses and pharmacists on medication error prevention
- Employ graduate pharmacists as clinical pharmacists to wards and ICUs

## Conclusion

Medication errors are common and result in significant patient harm globally. Majority of medication errors are preventable. Improving medication literacy of patients, training of health care staff and addressing system improvements including establishing medication incident reporting is needed. Learning from mistakes and taking actions to prevent them would reduce medication errors.

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## Answers to MCQs

- Question 1. a, b and c are false: b and c are regarded as “red flags” in patients with IBS
- Question 2. b is false
- Question 3. b is false. Type 3 consistently increases cardiac output and LV function, but there is no evidence of increased survival in heart failure

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# Treatment of irritable bowel syndrome

## Summary

Irritable bowel syndrome is a chronic functional gastrointestinal disorder that presents with abdominal pain, related to defecation, accompanied by a change in stool frequency or form. Despite its impact on a patient's quality of life, it has no effect on mortality.

A positive clinical diagnosis should be made if the characteristic symptoms are present and red flags are absent. Red flags should prompt specialist referral.

Consultations should be provided in an empathetic manner, addressing the concerns of the patient while providing reassurance.

Manipulating diet, with the assistance of a dietitian, is an appropriate initial treatment for irritable bowel syndrome. A low-FODMAP diet is an effective therapy.

Low-dose antidepressants improve symptoms but can be accompanied by adverse effects. Antispasmodic drugs have a limited role.

Psychological therapies and gut-focused hypnotherapy are effective if patients are willing to try them.

**Keywords:** constipation, diarrhoea, irritable bowel syndrome, low-FODMAP diet, psychological therapy

(*Aust Prescr* 2018; **41**: 145-9)

## Introduction

Irritable bowel syndrome is a functional gastrointestinal disorder meaning there are no biochemical or structural abnormalities on investigation.<sup>1</sup> However, it is treatable and it is among the most common complaints presenting to GPs<sup>2</sup> affecting about 9% of Australians.<sup>3</sup>

The syndrome is characterised by recurrent abdominal pain, related to defecation, and is associated with a change in stool frequency or form.<sup>4</sup> It is subtyped by the predominant stool form as follows:

- diarrhoea predominant (IBS-D)
- constipation predominant (IBS-C)
- mixed subtype (IBS-M).

The diagnostic criteria, referred to as the Rome criteria, are based on an expert consensus governed by the Rome Foundation (see Box 1).<sup>5</sup>

Given the broad definition of irritable bowel syndrome, it is likely to represent multiple different conditions, each developing from unique pathophysiological mechanisms.<sup>6</sup>

These include intolerance to particular foods, hypersensitivity to pain and psychosomatic manifestations of anxiety or stress. Other associated mechanisms include low-grade inflammation, altered microbiota, genetic factors and altered 5-HT (5-hydroxytryptamine) metabolism.

Irritable bowel syndrome can result in significant disability, reduced quality of life and impaired workforce productivity.<sup>7</sup> Fortunately, it is not directly associated with mortality<sup>8</sup> or an increased risk of gastrointestinal malignancies.<sup>9</sup>

## Diagnosis

Irritable bowel syndrome is not a diagnosis of exclusion. A positive diagnosis should be based on the presence of characteristic symptoms<sup>4</sup> (Box 1), and the absence of red flags. Patients with red flags should be referred for further investigation, including imaging or specialist review (Box 2).<sup>6</sup> A significant proportion of patients with irritable bowel syndrome may have symptoms that overlap with another functional gut disorder.

### Box 1 The Rome IV diagnostic criteria\* for irritable bowel syndrome

Recurrent abdominal pain, on average, at least one day per week in the last three months associated with two or more of the following criteria:

1. Related to defecation
2. Associated with a change in the frequency of stool
3. Associated with a change in the form (appearance) of stool

\* Criteria fulfilled for the last three months with symptom onset at least six months before diagnosis.

Source: reference 5

### Box 2 Red flags that require further testing or specialist assessment

Age over 50 years, no previous colon cancer screening and presence of symptoms  
Recent change in bowel habit in people over 50 years of age  
Evidence of overt gastrointestinal bleeding (i.e. melaena or haematochezia)  
Nocturnal pain or passage of stools  
Unintentional weight loss  
Family history of colorectal cancer or inflammatory bowel disease  
Palpable abdominal mass or lymphadenopathy  
Evidence of iron deficiency anaemia on blood testing  
Positive test for faecal occult blood

Adapted from reference 6

Initial testing should be minimally invasive. Full blood counts, urea and electrolytes, C-reactive protein and liver function tests would constitute reasonable initial investigations.

Coeliac serology should be considered as there is a significantly increased risk of coeliac disease among patients with symptoms that fit the Rome criteria for irritable bowel syndrome.<sup>10</sup> Genetic testing for coeliac disease is not recommended – it is unlikely to discriminate between irritable bowel syndrome and coeliac disease because more than 30% of the population share the HLA-DQ2/8 gene.<sup>11</sup>

The symptoms of irritable bowel syndrome share similarities with inflammatory bowel disease and gastrointestinal malignancies. The concern of organic gastrointestinal pathology, even in the absence of red flags, may prompt many clinicians to recommend an endoscopic assessment. There is no role for a faecal occult blood test to exclude gastrointestinal malignancy in patients with symptoms of irritable bowel syndrome.<sup>12</sup>

A normal faecal calprotectin test result, which measures intestinal inflammation, reduces the need for endoscopy to rule out inflammatory bowel disease.<sup>13</sup>

Understandably, many clinicians are not confident to make a diagnosis of irritable bowel syndrome without specialist assessment. However, clinicians should be reassured that patients presenting with symptoms of irritable bowel syndrome in the absence of red flags are extremely unlikely to be affected by serious organic illness.<sup>14</sup>

## **Treatment**

The treatment for irritable bowel syndrome should involve addressing the patient's concerns, and prescribing treatments that tackle the mechanisms underpinning their symptoms.

### ***The consultation***

An appropriately conducted consultation can be therapeutic for a patient with irritable bowel syndrome. However, only a minority of patients consult their GP, and an even smaller proportion seek specialist care.<sup>15</sup>

Clinicians should therefore recognise that patients who present with irritable bowel syndrome require a holistic consultation. A positive diagnosis and reassuring explanation of irritable bowel syndrome should be delivered in an empathetic manner, while allowing time for the patient to discuss their concerns. A randomised controlled trial showed patients who were given sham acupuncture were less likely to have adequate relief of irritable bowel syndrome symptoms compared with patients who received sham acupuncture combined with a 'warm empathetic' consultation (44% vs 62%,  $p < 0.001$ ).<sup>2</sup>

### ***Diet***

Many patients with irritable bowel syndrome report aggravated gastrointestinal symptoms related to specific foods.<sup>16</sup> This perception lends itself well to a therapeutic

manipulation of diet. However, clinicians should be mindful of overly restrictive eating patterns,<sup>17</sup> and dietary manipulation should be supervised by a dietitian.

### ***General dietary advice***

The UK's National Institute of Health and Care Excellence (NICE) recommends eating smaller frequent meals, avoiding trigger foods, and avoiding excess alcohol and caffeine. This diet has been found to be as effective as a low-FODMAP diet (low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols) for the diarrhoea-predominant irritable bowel syndrome.<sup>16</sup>

### ***Fibre***

Insoluble fibres are more likely to worsen abdominal pain and bloating in patients with irritable bowel syndrome.<sup>6</sup> However, soluble fibres such as psyllium improve symptoms, especially in patients with the constipation subtype.<sup>18</sup>

### ***Low-FODMAP diet***

Foods containing FODMAPs (which are short-chained carbohydrates) are poorly absorbed by the small intestine. This leads to an osmotic effect in the colon and excess gas production causing pain and diarrhoea. A low-FODMAP diet has been proven to significantly reduce symptoms related to irritable bowel syndrome compared to a regular Australian diet.<sup>19</sup> Patients with irritable bowel syndrome, especially those with the diarrhoea subtype, should consider a low-FODMAP diet as their initial therapy. Individual symptoms of pain and bloating seem to respond to this diet.

A dietitian-supervised low-FODMAP diet involves an exclusion phase where patients reduce FODMAP-containing foods over six weeks. If the patient reports a significant reduction in symptoms, FODMAP-containing foods can be carefully re-introduced over subsequent weeks. Remaining on an exclusively low-FODMAP diet in the long term has been shown to transform the intestinal microbiota to a potentially negative profile,<sup>19</sup> and therefore is not recommended.

### ***General lifestyle advice***

Symptoms of irritable bowel syndrome can be mitigated by regular exercise<sup>20</sup> which should be recommended in conjunction with dietary advice. The importance of sleep should also be discussed as improved quality of sleep has been found to control symptoms.<sup>21</sup>

### ***Medicines***

Drugs exclusively developed for irritable bowel syndrome are not available in Australia, unlike the USA and Europe. Most of the drugs used here were designed for other indications.

### ***Mebeverine and hyoscine***

Antispasmodic drugs have only modest effects in irritable bowel syndrome and have a limited role.<sup>22</sup> Although hyoscine has greater evidence for symptom relief,<sup>23</sup> it is



associated with significant adverse effects including constipation and dry mouth.

### *Peppermint oil*

Peppermint oil acts as an antispasmodic through smooth muscle calcium channel antagonism.<sup>24</sup> A systematic review found that it significantly reduces symptoms compared with placebo.<sup>25</sup>

### *Antidepressants*

Antidepressants can significantly reduce symptoms of irritable bowel syndrome.<sup>26</sup> They are purported to work by manipulating visceral hypersensitivity and abnormal central pain sensitisation.<sup>24</sup> Tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) have both demonstrated benefit.<sup>26</sup> Tricyclics are ostensibly used for the diarrhoea subtype due to their known adverse effect of constipation. Similarly, SSRIs may be better used for the constipation subtype due to their adverse effect of diarrhoea. Although SSRIs have been shown to be of benefit,<sup>26</sup> the exact dose and their use are not universally accepted for the treatment of irritable bowel syndrome.

It is important to advise patients that antidepressants are used for their neuropathic-pain-modulating effect, rather than for an antidepressant effect. Patients should take a low dose of the antidepressant every day for 4-6 weeks before assessing efficacy.

### *Rifaximin*

Rifaximin has a limited role in irritable bowel syndrome and it is not subsidised by the Pharmaceutical Benefits Scheme for this indication. It is a non-absorbed antibiotic that modestly reduces symptoms of non-constipating irritable bowel syndrome compared to placebo.<sup>27</sup> Despite theoretical concerns of developing persistent bacteria that are resistant to rifaximin, studies have not demonstrated this to be the case.

### *Probiotics*

Probiotics possibly have a role in irritable bowel syndrome but the dose and strain needed for benefit is not clear. Of the products available in Australia, the strains and doses are too varied to provide a meaningful recommendation based on evidence.<sup>28</sup>

### *Psychological therapies*

There are many psychological therapies that have been shown to improve or resolve symptoms in irritable bowel syndrome. These include cognitive behavioural therapy, multi-component psychological therapy and dynamic psychotherapy.<sup>26</sup>

Some patients recognise that their symptoms arise or are aggravated by stress and anxiety. For these patients, offering psychological therapies as a direct method to treat irritable bowel syndrome is a reasonable solution. A carefully timed and formulated referral to a psychologist

with expertise in functional gastrointestinal disorders improves the chance of a successful outcome.<sup>29</sup>

Many patients do not associate their symptoms with psychological disturbance, even if there appears to be an obvious clinical correlation. Offering psychological therapy for these people is unlikely to be therapeutic.

### *Gut-focused hypnotherapy*

Hypnotherapy has been proven to reduce symptoms of irritable bowel syndrome with sustained benefit for greater than five years.<sup>30</sup> A recent Australian trial showed that gut-directed hypnotherapy is as effective as a low-FODMAP diet.<sup>31</sup>

Patients should be advised that hypnosis is not as theatrical as it is portrayed in popular culture. It usually incorporates cognitive behavioural therapy and relaxation exercises administered by a psychologically trained hypnotherapist, typically over 10 weekly sessions.

### *Physical and behavioural therapies*

Pelvic floor dysfunction is underdiagnosed among patients with irritable bowel syndrome, especially those with the constipation subtype.<sup>32</sup> These patients either fail to relax the pelvic floor or paradoxically contract the pelvic floor muscles causing obstructed defaecation.<sup>33</sup> Through a technique referred to as biofeedback, physiotherapists with expertise can retrain patients to use their pelvic floor muscles appropriately. Patients are given visual or tactile awareness of involuntary bowel function in order to learn voluntary control.<sup>34</sup> Behavioural aspects that contribute to symptoms such as incorrect toileting posture, prolonged time spent in the toilet and the use of inappropriate cues to trigger the need to defecate are also addressed with exercises and biofeedback.<sup>35</sup> Selecting patients for this therapy is best determined by specialists with expertise in the diagnosis of irritable bowel syndrome.

### **Severe disease**

Some patients can present with a severe form of irritable bowel syndrome, resulting in multiple admissions to hospital and repeated investigations.<sup>15</sup> Despite what may appear to be debilitating symptoms, clinicians should avoid prescribing opioids for pain as it can cause narcotic bowel syndrome. These patients are best managed by a single gastroenterologist working with a multidisciplinary team including a psychologist.<sup>6</sup>

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### **Conclusion**

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Irritable bowel syndrome is a common chronic gastrointestinal condition. A positive clinical diagnosis is made using the Rome criteria, in the absence of red flags. Patients with red flags should be referred for further testing or specialist assessment.

Once the diagnosis is made, consultations should provide reassurance in an empathetic manner with time allocated to address the patient's concerns.

There are multiple therapeutic modalities that benefit patients with irritable bowel syndrome, including medicines, diet and psychologically based therapies.

*Conflict of interest: none declared*

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