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SA Pharmaceutical Journal

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SAPJ is aimed at the continuing professional development of the South African pharmacist in a variety of practice settings, including clinical pharmaceutical care practitioners in a community or hospital pharmacy environment, and pharmacists in academic and industrial practice.

The journal accepts specific clinical reviews on self-medication topics (symptomatic therapy) and information on prescription medication (therapy in clinical context), and provides pharmacists with essential information for referring customers for early medical attention should it be required. SAPJ further recognises that the role of the pharmacist continually evolves to meet the needs of the population. An example of this is the provision of accessible, basic primary health care services in community pharmacies.

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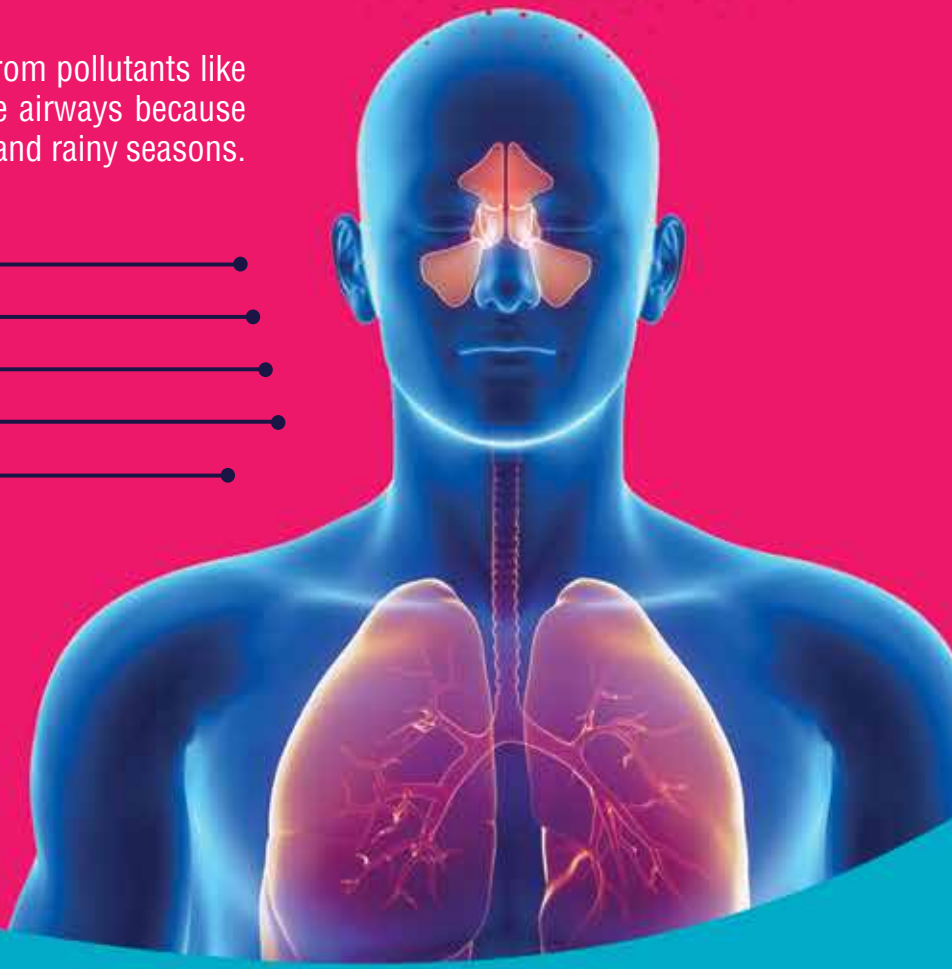

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President's Message

Navigating through a world full of turmoil

Joggie Hattingh
PSSA President

It seems like the entire word is in turmoil. Lately our lives were immensely disrupted by Covid-19 and the ensuing measures taken to limit the spread of it. Then the riots of 2020 impacted heavily on our country and our profession, only to be followed by the Ukrainian war and the resulting impact it has had worldwide.

Locally we are under siege with rising interest rates, rising fuel prices and rising cost of living, whilst salaries and dispensing fees simply do not keep up with the runaway trajectory of inflation. Meanwhile we are still reeling under the impact of the scale of plundering of state assets and the continued denial of the guilty parties. All of this leaves us stunned by shockwave after shockwave of changes we have to absorb. Changes in our beliefs, changes in our allegiance and changes in our ability to cope and survive.

Change is never easy, and when it is forced upon us in such quick succession as is happening right now, it is downright scary. Yet, tranquility is a choice, so is anxiety! This means that even though we live in the turmoil, if we want to be peaceful within, WE CAN! We do have a choice.

It is a good reminder that we can contribute to tranquility and peace with clear and concise communication. It is said that "five minutes of communication can save a year's worth of turmoil and misunderstanding". How often do we see that poor communication unnecessarily contributes to the chaos in our lives?

Because the word today is so full of turmoil, many people are disgruntled and unhappy, as they feel that it is not through their own fault that it is so, yet it affects them severely. I tried to teach my children from an early age that life is not fair, nor is it perfect. Bad things happen to good people even though they are not at fault. That is just the way it is. However, if you dwell on anger and resentment and the unfairness of life, it will only get worse.

While we may not be able to stop what happens to us, we can change how we look at it! This may seem like a futile exercise, but though it is a small start, this one act can change your whole life and then affect the world we live in! Let us start to look for solutions for the problems in our lives and start to support those around us who are also struggling. We may find that the more we look to fix what is wrong, the more hope we have in our lives and then this hope will rub off onto others. While we may not be able to change the world alone, together we will spread a message of hope and faith in our future and our ability to overcome whatever is thrown at us.

Let us start doing so as a family of pharmacists and let us also extend this positivity into our communities. We were not placed on this earth to be self-centered and self-serving individuals. Our purpose in life is to enrich and infuse others' lives with our caring and humility and to spread the hope we carry inside us.

The fight for the rights of patients and their access to healthcare

A brief explanation of the two legal issues in which the Independent Community Pharmacy Association (ICPA) is currently involved.

ICPA to have its day in the Constitutional Court

Following a protracted legal battle in the Western Cape High Court and the Supreme Court of Appeal (SCA) between ICPA and the Clicks Group, ICPA was given a date to put its case on pharmacy ownership and patient rights before the apex Court.

The Pharmacy Act empowers the Minister of Health to prescribe who may own a pharmacy and the conditions under which such person may own a pharmacy. Regulation 6(d) of the Ownership Regulations is to the effect that any person who owns a community pharmacy may not also own or be the holder of any direct or indirect beneficial interest in a manufacturing pharmacy.

The obvious purpose of the regulation was to ensure that pharmacists or the owners of community pharmacies do not have a vested interest in the medicines which are dispensed or recommended to consumers.

ICPA won in the High Court but lost 4-1 in the SCA. In the dissenting judgment by Makgoka JA in the SCA, i.e. not the majority judgement, it was held that

> "*Another danger is that if pharmacies are permitted to create their own affiliated manufacturers whom they control, directly or indirectly, they would directly be involved in setting prices and have strong incentives to keep those prices high. There is an inherent conflict of interest when a pharmacist is employed and remunerated by an entity which forms part of a group which also owns or has an interest in a manufacturing entity. The high court further pointed out, an entity having interests in both types of pharmacies would gain financially if the manufacturing pharmacy's products are promoted by the pharmacists in the community pharmacies over other products. This could result in consumers not getting the best quality product at the best price. Products which are not strictly needed might be recommended and sold. The conflict of interest could also result in the manufacturing pharmacy favouring community pharmacies belonging to the same group above outside or independent pharmacies. This might affect the availability of products to customers.*"

ICPA maintains that a conflict of interest exists within the Clicks Group as Clicks owns more than 600 pharmacies and also owns a manufacturing pharmacy, Unicorn Pharmaceuticals. The Unicorn brand has many generic medicines under its label which are only available to Clicks Pharmacies. ICPA has set out in its court papers why it believes that the Clicks Pharmacies actively promote their own brands and why it says that Clicks' pharmacists are incentivised to promote their Unicorn brand. ICPA contends in the Court case that Clicks' pharmacists' performance appraisals require that a certain percentage of sales are own brand sales. If so, this might put some of their pharmacists in a difficult position, either to recommend a medicine they believe is best suited to the patient or an alternative Unicorn own brand to ensure his/her performance appraisal is favourable. Another challenge is that certain medicines are not easily substitutable, such as certain heart medicines and many anti-epileptic medicines. If a patient is stabilised on a Unicorn brand of one of these medicines, he or she is effectively restricted to using Clicks Pharmacies only as other pharmacies cannot purchase Unicorn brand of medicines.

ICPA will argue in the Constitutional Court proceedings, which are set down for 1 September 2022, that the Clicks corporate structure is in contravention of the Pharmacy Act and Regulations, and that if Clicks are allowed to continue in this manner, then they are infringing on individuals' rights to access to health care services.

Undesirable business practices and penalty co-payments

On 23 April 2021, the Council for Medical Schemes (CMS) published a landmark notice which declared certain practices by medical schemes in selecting designated health care providers and imposing excessive co-payments on members as irregular and/or undesirable practices by the medical schemes. The dispute with CMS, but more specifically the medical schemes practices, dates back to before 2013. ICPA's unwavering fight for patient rights led to successfully launching and winning two appeal processes against the statutory council, which ultimately resulted in the publication of this declaration. ICPA contended that certain medical schemes select Designated Service Providers (DSPs) in a non-transparent and discriminatory manner without considering applications to join the network from all interested service providers. Further these schemes then effectively coerce their members to utilise these DSPs or face punitive co-payments. In some instances, vulnerable patients with complex treatment regimens are forced to utilise a single pharmacy courier service for all their chronic medicines.

Unfortunately, instead of abiding by the declaration, some of the medical schemes have decided to appeal the publication of the directives. ICPA have been advised by CMS that the appeal by the medical schemes is likely to be heard in November 2022.

The PSSA/Alpha Pharm distance learning programme 2022

The PSSA/Alpha Pharm distance learning programme continues to offer pharmacists useful, practical, up-to-date information that enables them to provide optimal pharmaceutical care to their patients.

Module 4, 2022 – Urinary tract infections

Urinary tract infections are common in community practice worldwide and are usually caused by *Escherichia coli*, which is responsible for approximately 80% of all UTIs.

Most UTIs in women are acute uncomplicated cystitis or 'bladder infections', which may not be considered a serious condition but can significantly affect the patient's quality of life. UTIs among women are extremely common, particularly during the reproductive years.

Pyelonephritis is a bacterial infection of the kidney. In 95% of cases, the cause is the ascension of bacteria through the urinary tract to the kidney. Pyelonephritis is a serious infection with the risk of bacteraemia (the presence of bacteria in the bloodstream).

UTIs are becoming increasingly difficult to treat, owing to the rapid spread of drug resistance among causative organisms.

This module discusses urinary tract infections, focusing on acute cystitis and pyelonephritis in women. After completing this module, you will:

- Know the risk factors for UTIs in women.
- Be able to recognise the symptoms of UTIs and refer patients to the doctor, if necessary.
- Understand the role of urinalysis using urine dipstick testing and be able to explain what positive and negative results mean, referring patients for further evaluation as appropriate.
- Be able to give advice about the OTC management of UTI symptoms.
- Be able to play a key role in ensuring appropriate antibiotic selection and use for the treatment of community-acquired UTIs.

For more information about this programme, contact Gill or Glynis at Insight Medicine Information on 011 706 6939 or email: cpdalphapharm@insightmed.co.za.

The PSSA/Alpha Pharm clinical education programme 2022 for pharmacy staff

The PSSA/Alpha Pharm pharmacy staff clinical education programme continues to offer front-shop assistants or pharmacist's assistants up-to-date information that enables them to provide optimal pharmaceutical care to their patients. All pharmacy staff need to be familiar with the use of unscheduled medicines and should be reminded of when it is necessary to refer the patient to the pharmacist.

Module 4 – Understanding urinary tract infections

Urinary tract infections happen when bacteria get into the urethra and travel up into the bladder. If the infection stays in the bladder, it is called a bladder infection or 'cystitis'. If the infection travels up past the bladder and into the kidneys, it is called a kidney infection or 'pyelonephritis'. Bladder and kidney infections are both types of urinary tract infections.

Most cases of bladder infection in women are uncomplicated or 'simple cystitis' and are easily treated with a short course of oral antibiotics. Kidney infections can also usually be treated at home with antibiotics, but treatment typically lasts longer. In some cases, kidney infections must be treated with intravenous antibiotics, which need to be given in the hospital.

This module discusses UTIs in women so that the pharmacy front shop staff member can recognise the symptoms and refer women appropriately for further medical attention. Some medicines and products are available for over-the-counter (OTC) treatment of UTI symptoms. These products may be used when symptoms are mild or until the patient can consult her doctor.

If you would like to participate in the PSSA/Alpha Pharm pharmacy staff clinical education programme, please contact Gill or Glynis for further information on 011 706 6939 or email: cpdalphapharm@insightmed.co.za.

A message from the PSSA YPG Steering Committee 2022/23

Our message to you!

Around 1980, Bill Gates said: "A computer on every desk and in every home," certain of the impact that his invention would have on society. As the newly elected steering committee of the PSSA YPG, we would like to allude to Mr Gates' passion and fix our term to the following quote: "Young pharmacists – connected, engaged, empowered, and inspired!". As we are slowly easing into the second month of our term, we are currently developing our year plan and we would like to engage the voices of all young pharmacists nationwide and develop activities that will be beneficial to you. We encourage you to contact us via our email and social media pages listed below and share your thoughts with us so that we can tailor this year to your needs. We look forward to serving you!

Nelson Mabusela
Chairperson

Roslita da Silva
Project co-ordinator

Ntombizodwa Luwaca
Public relations officer

Professional Innovation Project 2022 Winner – Luke Zondagh

We would like to congratulate Luke Zondagh on presenting the best professional innovation project titled: Discovery of novel dual-acting neuroprotective scaffolds: SIRTI activators and GSK3β inhibitors. Below find an abstract of his project.

Discovery of dual acting neuroprotective scaffolds using various computational and biological evaluation techniques. The project will be used to introduce the B.Pharm final year students to various computational software and skills that are in line with South Africa's digital and future skills strategy. The project also introduces the research field bioinformatics to the students which is supported by the National Institute for Theoretical Physics and Computer sciences.

Luke's reflection on winning the PIP grant

"I am delighted and privileged to have been awarded the Professional Innovation Project (PIP) grant. The PIP grant will greatly assist me in driving my research project in finding dual-acting GSK3B inhibitor – SIRT1 activator anti-Alzheimer's agents. Throughout the project, I will be collaborating with final year pharmacy students where I have the opportunity to teach them various aspects and techniques used within the pre-clinical drug discovery pipeline. My personal goal for this project is to continue to develop as an early-career pharmaceutical scientist while simultaneously demonstrating that undergraduate pharmacy research can be competitive and successful."

Feel free to reach out to us at
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Young Pharmacists' Group of PSSA

Young pharmacists – connected, engaged, empowered and inspired!

An overview of fixed-dose combinations of antihypertensive drugs in South Africa

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Abstract

Hypertension is a pressing global health issue, contributing to an increase in cardiovascular risk, as well as being the most common condition seen in South Africa. Lack of compliance with the prescribed therapy is one of the largest obstacles to achieving goal blood pressure in antihypertensive patients. The complexity of the drug therapy is a very important factor that is associated with noncompliance, as most patients require treatment with two or more drugs. The use of fixed-dose combination (FDC) therapy has various advantages, including simplification of the regimen, resulting in improved adherence. However, there are also disadvantages, e.g. the inability to provide individualised dose flexibility. This article provides an overview of available FDC therapy for hypertension in South Africa and the rational use thereof, by taking into account each combination's complementary action, efficacy, safety and tolerability.

Keywords: antihypertensives, fixed-dose combination, hypertension

Updated from: *S Afr Fam Pract.* 2014;56(4):206-211

S Afr Pharm J 2022;89(5):10-16

Introduction

Hypertension is a haemodynamic disorder, associated with a rise in peripheral vascular resistance that, in turn, can lead to myocardial infarction, renal failure, strokes and death, if not identified early and treated properly.[1-3] It is the most common condition seen in South Africa, estimated to have caused 46 888 deaths and 390 860 disability-adjusted life years in 2 000 disability-adjusted lives in the year 2000.[4] Many patients with hypertension do not attain the desired blood pressure (BP) goal of < 140/90 mmHg. A reduction in BP is considered to be the primary determinant of a reduction in cardiovascular risk. The complex relationship of genetic and environmental elements includes factors associated with high BP, and can lead to activation or inhibition of one or more of the processes involved in its control.[1,3,5-7] Dietary factors and physical inactivity contribute to the genetic predisposition, while environmental factors include smoking, drinking, obesity and alcohol. This means that hypertension is a preventable cause of morbidity and mortality. The advantages of leading a healthy lifestyle, including a controlled diet and regular exercise for all populations with hypertension cannot be stressed more. The primary goal of treatment is to abolish the risks associated with hypertension, without reducing a patient's quality of life.[1-4]

The renin-angiotensin-aldosterone system (RAAS), as well as the sympathetic nervous system is involved in regulating arterial pressure. Hypertension is usually multifactorial, interfering with different pressor mechanisms. Thus, acting on several physiological systems improves blood pressure goal attainment rates. Three main factors that determine BP include renal sodium excretion and the resultant plasma and total body volume, as well as vascular tone and cardiac performance. Each of these factors controls determinants of BP, like cardiac output, intravascular volume and systemic vascular resistance. RAAS plays a central role in elevating BP through these mechanisms. This system regulates the secretion of renin, with feedback systems from sodium balance, arterial BP levels and angiotensin II. The direct vasoconstrictor effect of angiotensin II, resulting from the secretion of renin, can increase systemic vascular resistance, and salt and water retention can again lead to an increase in the extracellular blood volume. The rationale for combining drugs from different classes lies in reaching the goal BP more rapidly, as each drug works at a separate site, blocking different effector pathways.[1,3,7] An overview of the RAAS system is presented (Figure 1).

One of the largest obstacles to achieving goal BP in antihypertensive patients is the patients themselves, the challenge being lack of adherence to the prescribed therapy. BP variability increases with increasing BP levels. The complexity of the drug therapy is an important factor that is associated with noncompliance as the majority of patients need treatment with more than one agent. Multiple clinical trial evidence supports the use of combination therapy, indicating that it results in better clinical outcomes than monotherapy. Comorbid conditions, such as diabetes mellitus, impose an even greater pill burden, making it critical to address the adherence challenge in order to achieve maximum clinical benefit.

Studies have demonstrated that high adherence to antihypertensive therapy (AHT) is associated with a significant decrease in cardiovascular events (CVE), and also results in decreased hospitalisation rates and better cost-effectiveness, compared with low adherence. Additional target organ protection is also provided with 24-hour BP control. Thus, major long-term benefits are realised in patients who comply with their AHT.[5-10]

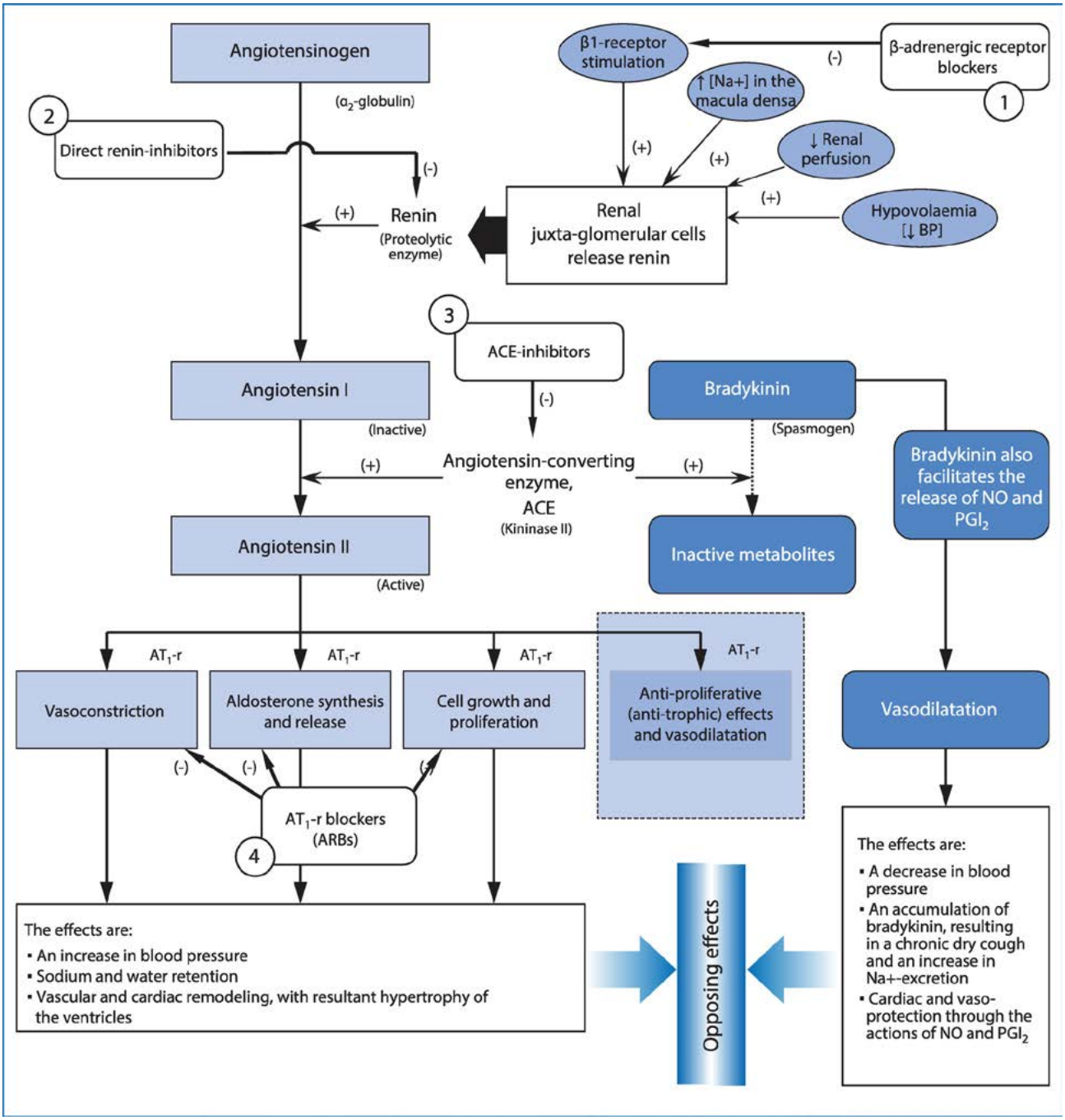

Figure 1: Diagram of the renin-angiotensin-aldosterone system showing the sites of action of the β-adrenergic receptor blockers, the direct rennin inhibitors, the angiotensin-converting enzyme inhibitors and the angiotensin II receptor blockers.[22]

Rationale for combination therapy

The development of single-pill combinations of two antihypertensive agents, commonly known as a fixed-dose combination (FDC), is the solution to overcoming nonadherence.[9,11] Combination therapy has the ability to target different physiological systems, there is a synergistic pharmacological effect at lower doses of individual agents and it also attempts to block counter-regulatory responses, achieved through blockage by a single agent.[1,10] This is achieved as hypertension affects multiple regulatory systems, and combining more than one agent causes interference in multiple pathways, as well as a reduction in the activation of counter-regulatory mechanisms.[9] A reduction in metabolic consequences can also be seen because of the use of lower doses of single-drug components. BP control in a large population is often only reached with a combination of drugs from different classes.[1,3,6,12] Components in FDCs can be designed to counteract each other's side-effects, resulting in an overall neutral effect. Also, BP goals may be reached earlier than would be the case with monotherapy. Furthermore, as the two components can be given at lower dosages, most antihypertensive drugs produce dose-dependent adverse effects.[3,7-10] The convenience, tolerability and simplicity associated with FDCs help to accomplish sustained BP targets over a long period, which can result in advantages with

Table I: Rational blood pressure goals according to the JNC 8[2]

Populations aged < 60 years	Populations of all ages with diabetes	Populations of all ages with CKD, with or without diabetes	Populations aged > 60 years
< 140/90 mmHg	< 140/90 mmHg	< 140/90 mmHg	< 150/90 mmHg

CKD – chronic kidney disease

Table II: Advantages and disadvantages of fixed-dose combination therapy[10,20]

Advantages	Disadvantages
Simplification of the regimen < 140/90 mmHg	Individualised dose flexibility is lost
Improved adherence	Specialised dosing is lost when treating specific co-morbid conditions
Reduced pill burden	The likelihood of dose-dependent reactions is increased
There is a potential reduction in costs, when compared to taking the individual drugs separately	

respect to cardiovascular outcomes and reducing the risk of a stroke.[1,9,11,13-16]

Thus, the complexity of treatment regimens is reduced with FDCs and is associated with better compliance and persistence with treatment, motivating patients to adhere to lifelong therapy.[1,10]

The Eighth Joint National Committee (JNC 8) recommends selection from four specific medication classes, known as:

- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin-receptor blockers (ARBs)
- Calcium-channel blockers
- Diuretics[2]

BP goals are based on age, diabetes and chronic kidney disease.

Table I provides the different BP goals recommended by the JNC 8.

Most patients require two or more drugs to reach optimal control of their BP, as combining drugs from complementary classes provides approximately a five times greater antihypertensive effect than increasing the dosage of a single drug.

Thus it is recommended that:

- Therapy is initiated with two drugs from different classes when the BP is > 20 mmHg (systolic) or > 10 mmHg above the diastolic target.
- A third drug is selected when the target BP is still not reached, titrating the third drug up to the maximum recommended dose. (This excludes the combined use of an ACE inhibitor and an ARB.)
- Consideration is given to initiating AHT with more than one drug in patients at high cardiovascular risk, identified by increased BP and other risk factors.
- Low-dose combination therapy is used as the initial treatment. A meta-analysis showed that this resulted in greater cardiovascular benefits than the initiation of monotherapy.[2,3,14,17-19]

Advantages and disadvantages of fixed-dose combinations

The use of combination therapy has various advantages, e.g. a convenient dosing format and improvement of patient compliance.[10,20] There are also disadvantages when compared to single-drug therapy. Table II provides a summary of the advantages and disadvantages of FDC therapy.

Available options for combination therapy

Combined drug therapy started in 1960 with the combination of hydrochlorothiazide (HTCZ) and triamterene.[16] Benefits from

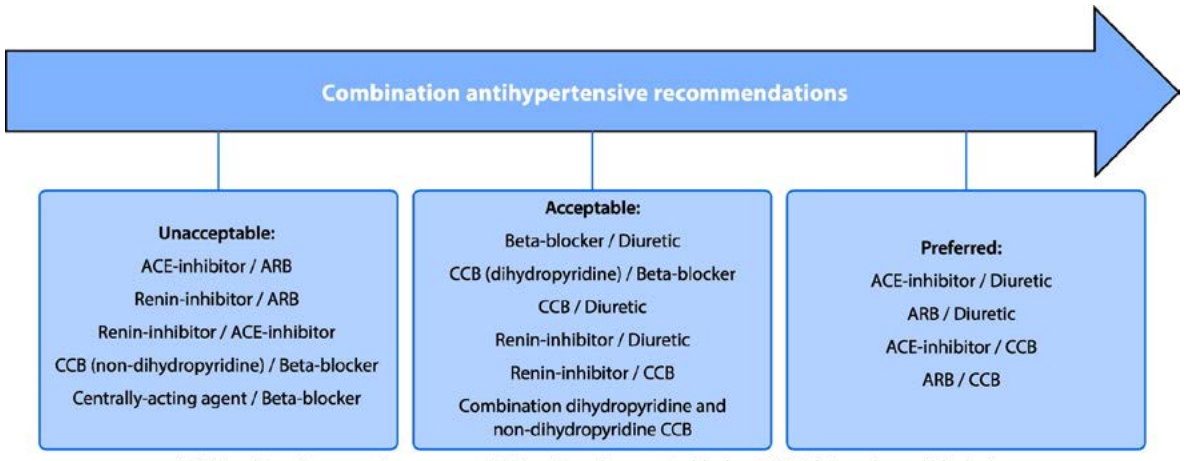

Figure 2: Recommended antihypertensive combination therapy

CONTROL NOW WITH SINGLE PILL COMBINATIONS (SPC) TO PREVENT COSTLY CO-MORBIDITIES RELATED TO UNCONTROLLED HYPERTENSION

WHEN TREATING PATIENTS WITH HYPERTENSION, TWO TREATMENTS ARE OFTEN NOT ENOUGH.

Patients may require 3 or more antihypertensive agents to achieve blood pressure control. The most rational combination appears to be a RAAS-blocker, a CCB and a diuretic at effective dose.[1]

The evidence shows that single pill combinations simplify treatment and improves outcomes[1,2,3,4]

STARTING

Initial two-drug combination therapy is more effective at reducing blood pressure than monotherapy[1]

SWITCHING

Combinations are widely available in a single pill and in a range of doses, facilitating simplification of treatment, flexible prescribing, and uptitration from lower to higher doses.[1]

Non-adherence was **<10%** with a single pill[1]

Rising to **~20%** with two pills[1]

~40% with three pills[1]

with very high rates of partial or **complete non-adherence** in patients receiving five or more pills[1]

Copalia(Valsartan/Amlodipine)
- provides effective control when dual therapy is required[5,6,7]
- persistent 24 hour blood pressure reductions[8]

Co-Copalia(Valsartan/Amlodipine/Hydrochlorothiazide)
- provides effective BP control when triple therapy is required[7,9]

Copalia and Co-Copalia reduces blood pressure in a diverse patient subgroup, in a real-world setting.*[9]

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RAAS, Renin-Angiotensin-Aldosterone-System; **CCB,** calcium channel blocker; **SPC,** single pill combination; **BP,** blood pressure

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Table III: Fixed-dose combinations available in South Africa[23]

Combination	Fixed dose combination examples	Trade name
ACEI–CCB	Trandolapril/Verapamil	Tarka®
ARB–CCB	Amlodipine/Valsartan	Exforge®, Copalia®
	Valsartan/HCTZ/Amlodipine	Co-Exforge®, Co-Copalia®
	Telmisartan/Amlodipine	Twynsta®
ACEI–diuretic	Captopril/HCTZ	Zapto-Co®
	Benazepril/HCTZ	Cibadrex®
	Enalapril/HCTZ	Co-Renitec®
		Pharmapress Co®
	Lisinopril/HCTZ	Adco-Zetomax®
		Hexal-Lisinopril Co®
		Lisinopril Co Unicorn®
		Lisoretic®
		Lisozide®
	Quinapril/HCTZ	Accumax Co®
		Accuretic®
		Adco-Quinaretic®
	Perindopril/Indapamide	Acesyl Co®
		Ariprel Plus®
		Coversyl Plus®
		Pearinda Plus 4®
		Perindopril Co Unicorn®
		Preterax®
		Prexum Plus®
		Vectoryl Plus®
ARB–diuretic	Irbesartan/HCTZ	Co-Irbewin®
		Coaprovel®
		Isart Co®
	Losartan/HCTZ	Ciplazar Co®
		Cozaar Comp®
		Fortzaar®
		Hytenza Co®
		Lohype Forte Plus
		Losaar Plus®
		Losacar Co®
		Losartan Co Unicorn®
		Lozaan Co®
		Netrasol Co®
		Sartoc-Co®
		Zartan Co®
	Telmisartan/HCTZ	Co-Micardis®
		Co-Pritor®
	Valsartan/HCTZ	Co-Diovan®
		Co-Diovan Plus®
		Co-Migroben®
		Co-Tareg®
		Co-Tareg160 Plus®
		Co-Zomevek®
β-adrenoceptor antagonist diuretic	Atenolol/chlortalidone	Tenchlor®
		Tenoretic®

ACE – angiotensin-converting enzyme, ARBs – angiotensin-receptor blockers, HCTZ – hydrochlorothiazide

their complimentary action result from the use of combination antihypertensive drugs.[10] However, the number of combinations is extensive, and is thus subdivided into preferred combinations, and acceptable, unacceptable or ineffective combinations. This subdivision is based on the outcome of the combination, the efficacy of the antihypertensive drug, and its safety and/or tolerability[1] (Figure 2). An overview of the available combinations in South Africa is presented in Table III.

Preferred combinations

Renin-angiotensin-aldosterone system inhibitors and calcium-channel blockers

Different combinations included under this group include the combination of an ACE inhibitor, ARB, or direct renin inhibitor with a calcium-channel blocker. The rationale behind this combination lies in the management of the side-effects between the two pharmacological groups:[1,3,10,16]

- The RAAS blocker counteracts the calcium-channel blocker-induced activation of the sympathetic nervous system, e.g. tachycardia, and the RAAS.
- Calcium-channel blockers cause a negative sodium balance which adds to the antihypertensive effects of the RAAS blocker.
- The RAAS clocker minimises the dose-dependent peripheral oedema caused by the calcium-channel blockers.

Until recently, FDCs of the calcium-channel blockers and a RAAS inhibitor have only been available with the use of an ACE inhibitor and calcium-channel blocker combination. This subsequently changed with the development of a combination of an ARB plus amlodipine.[16] However, similar end-points have been illustrated with ACE inhibitors and an ARB when used in combination. The ACE inhibitors were shown to be more cardioprotective, while the ARBs conferred better stroke prevention.[1]

Of the calcium-channel blockers, amlodipine seems to be best choice in terms of the dihydropyridine calcium-channel blocker, with its distinctive pharmacokinetics and pharmacodynamics:[7,16]

- A long half-life of 35 hours, thereby adequately controlling BP over 24 hours and allowing once-daily dose administration.
- The reduced incidence of cardiovascular events.
- Improved vascular structure, e.g. intima-media thickness of the carotid arteries.

The combination of ACE inhibitor with a calcium-channel blocker is beneficial in a patient with comorbid conditions, such as hypertension and diabetes. The combination of an ARB and a calcium-channel blocker has advantages beyond BP lowering, i.e. on the morbidity and mortality of patients with hypertension and other comorbid conditions.[10]

Calcium-channel blocker, ARB and a diuretic

Three antihypertensive agents are combined in a film-coated tablet (Co-Copalia) that complement each other to manage hypertension. These tablets contain amlodipine (dihydropyridine calcium-channel blocker [DHP-CCB]), valsartan (angiotensin II receptor blocker [ARB]), and a thiazide diuretic, hydrochlorothiazide (HCTZ). This formulation is indicated for the treatment of hypertension in patients stabilised on the individual agents given at the same doses and not for the initial therapy of hypertension.

Renin-angiotensin-aldosterone system inhibitors and diuretics

The majority of available FDCs is either an ACE inhibitor or an ARB inhibitor with a low-dose thiazide-type diuretic, usually a HCTZ.[16] The diuretics reduce the intravascular volume, thereby activating the RAAS, thus producing vasoconstriction with salt and water retention. This is antagonised by the RAAS inhibitor.[1,3] The addition of the RAAS inhibitor also counteracts diuretic-induced hypokalaemia and glucose intolerance.[1,3] The combination of perindopril and indapamide has been shown to reduce the incidence of strokes in the elderly by 30%.[1]

Acceptable combinations

Beta blockers and diuretics

The combination of beta blockers and diuretics results in similar side-effects that may augment the likelihood of the development of glucose intolerance, fatigue, sexual dysfunction and the onset of new diabetes.[1] Earlier literature suggesting that a β blocker should be used in patients with a diuretic was demonstrated to be inferior to the use of a calcium-channel blocker or a potassium-sparing diuretic in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) study.[1,21]

Calcium-channel blockers and diuretics

The use of amlodipine with a thiazide has the risk of producing new-onset diabetes and hyperkalaemia. However, the use of amlodipine, compared to that of valsartan, results in a similar reduction in both morbidity and mortality, thus the combination may be classified to be acceptable.[1,3]

Dual calcium-channel blockade

The combination of a dihydropyridine and verapamil plus diltiazem reduces BP, without augmented side-effects. This combination may be useful in patients with documented angio-oedema (that developed from RAAS inhibitors) and advanced renal failure with the risk of hyperkalaemia. No long-term safety studies are as yet available.[1]

Unacceptable or ineffective combinations

Dual renin-angiotensin-aldosterone system blockade

The combination of an ACE inhibitor and an ARB does not show any added BP lowering against using either one as monotherapy. The combination does not have any improved cardiovascular end-points, just a small BP reduction of 2.4/1.4 mmHg, when compared to using either an ACE inhibitor or an ARB on its own. The

combination also results in more side-effects than monotherapy on its own.[1,3]

Renin-angiotensin-aldosterone system blockers and beta blockers

There are no known additional BP reduction rates following the combination of RAAS blockers and beta blockers in the treatment of hypertension. Thus, this combination should not be used for that purpose. However, it has been shown to reduce reinfarction rates and to be cardioprotective in patients suffering from a myocardial infarction or with heart failure.[1,3]

Beta blockers and antiadrenergic drugs

The combination of a β blocker and an antiadrenergic drug, such as clonidine or methyldopa, does not have any additional beneficial effect on BP end-points. On the contrary, they may even produce a rebound effect in the BP, when discontinued abruptly. Also the combination can also cause a bradycardia or a heart block.[1,3]

Conclusion

The primary goal of reducing BP is to decrease the long-term risks of cardiovascular morbidity and mortality. The use of FDC therapy as first-line treatment may help to achieve these goals as most patients with hypertension require more than one drug.

The JNC 8 guidelines provide evidence-based recommendations for the management of hypertension. Similar treatment goals are defined for all hypertensive populations. The rationale is < 140/90 mmHg, except for some subpopulations when the evidence review supports different goals. For example, the JNC 8 recommends a target BP < 150/90 mmHg for populations aged 60 years and older. Selection from the four specific medication classes is recommended, i.e. the ACE inhibitors, or ARBs, calcium-channel blockers or diuretics. The use of combination antihypertensive drugs benefits from the complimentary action of the different combined classes. However, the number of combinations is extensive, and is thus subdivided into preferred combinations, and acceptable, unacceptable or ineffective combinations. The preferred recommended antihypertensive combinations are an ACE inhibitor combined with a diuretic, an ARB plus a diuretic, an ACE inhibitor in combination with a calcium-channel blocker and an ARB plus a calcium-channel blocker. These combinations are the most acceptable based on the outcome of the combination, their efficacy, safety and tolerability.

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Allergic rhinitis

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Abstract

Allergic rhinitis involves an inflammatory response of the nasal mucous membranes and is thus classically characterised by nasal congestion, itching, a runny nose and sneezing. However, multiple ear, nose and throat organs may be involved, each contributing their own additive signs and symptoms and risk for complications. The classification of allergic rhinitis is now based on the symptom duration and severity and no longer annual seasons. The golden standard remains the use of intranasal corticosteroids, despite the availability of several other treatment options. This article will explore the pathophysiology, classification, sign and symptoms and the management of allergic rhinitis.

Keywords: allergy, antihistamine, allergic rhinitis, corticosteroids, decongestants, rhinitis

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Pathophysiology

During an episode of allergic rhinitis, mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils present in the nasal lining resulting in an inflammatory response. This response is due to allergens such as dust, pollen, moulds and animal dander. The T cells cause the release of immunoglobulin (IgE), which results in histamine and leukotrienes that cause arteriolar dilation, increased vascular permeability, itching, rhinorrhea (runny nose), mucous secretion and smooth muscle contraction.[1] This is the immediate reaction. The late phase reaction is the release of eosinophilic infiltrates, which presents as hyposmia, chronic obstruction, post-nasal mucous discharge and nasal hyperreactivity.

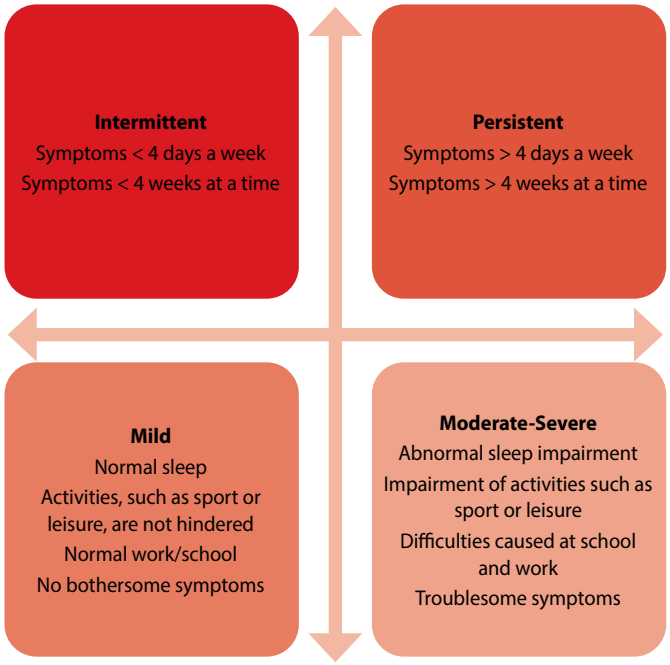


Figure 1: Classification of allergic rhinitis[1,2]

Classification of allergic rhinitis

Traditionally, allergic rhinitis was classified as either seasonal (hay fever) allergic rhinitis that occurs during spring and is caused by specific allergens such as pollen, grasses and weeds, or as persistent allergic rhinitis that occurs all year round and is in response to non-seasonal allergens such as dust mites, animal dander and moulds. Table I provides some of the common risk factors for allergic rhinitis. However, due to patients not fitting into the above descriptions and sometimes having both seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR), the classification has been modified as per the Allergic Rhinitis and its Impact on Asthma guideline (ARIA). The classification is now based on symptom duration (intermittent or persistent) and severity (mild, moderate or severe), see Figure 2.[1,2]

Table I: Risk factors for allergic rhinitis[2,3]

- Atopic diseases such as allergic rhino-conjunctivitis, asthma, atopic dermatitis, food allergies (typically genetic)
- Ethnic origin other than white European
- High socio-economic status
- Environmental pollution
- Birth during pollen season
- No older siblings
- Late entry into nursery or preschool education
- Heavy maternal smoking during the first year of life
- Exposure to indoor allergens such as animal dander and dust mites
- High concentrations of serum IgE before the age of 6 years
- Early introduction of foods or formula

Signs and symptoms

Allergic rhinitis is defined as inflammation of the mucous membranes of the nose, sinuses, pharynx, eyes, eustachian tubes and the middle ear due to allergens. Because an inflammatory response is responsible for this condition and the nose is inevitably involved, the classic symptoms are characterised by sneezing,

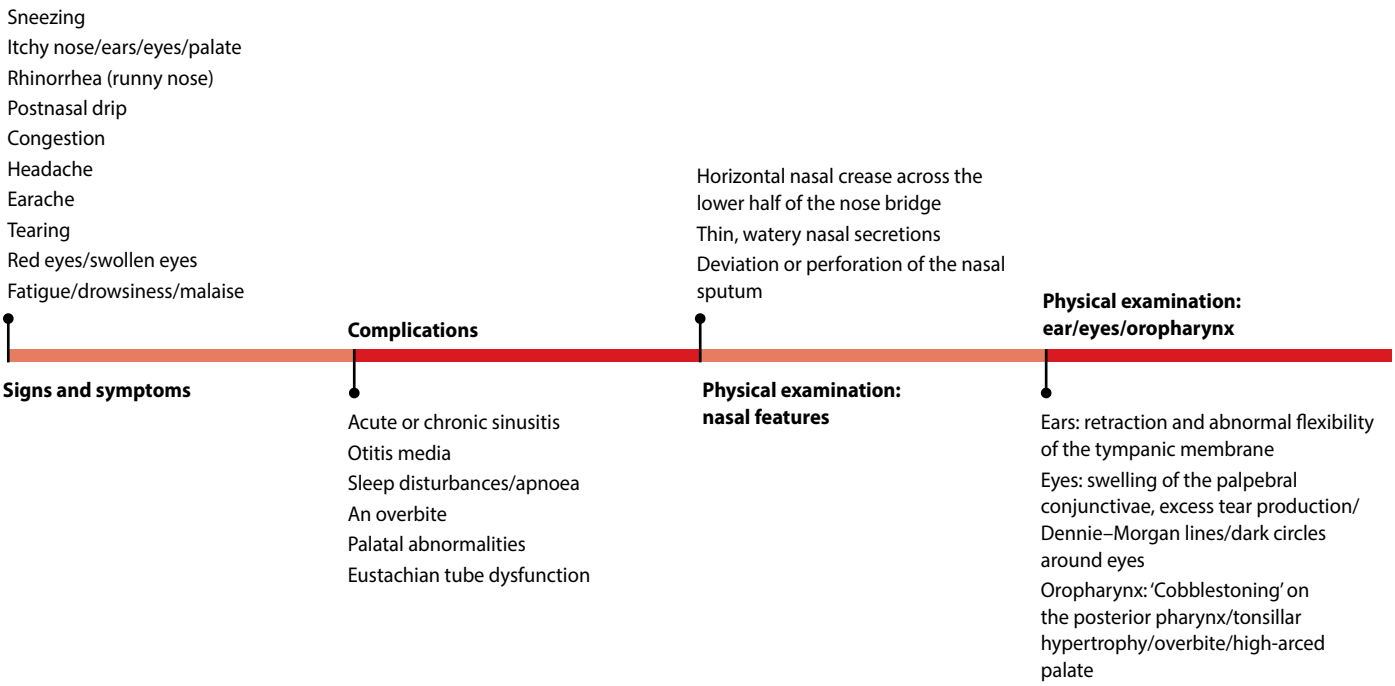


Figure 2: Signs, symptoms and complications of allergic rhinitis[4,5]

nasal congestion, itching and the discharge of a thin layer of nasal mucus fluid (rhinorrhea), as outlined in Figure 1.[4]

Allergic rhinitis is not a life-threatening condition, but due to the involvement of multiple ear, nose and throat (ENT) organs, individual complications may arise, which may contribute to significant impairment of the quality of life (Figure 2).

Management

The main goal in the management of allergic rhinitis is to provide symptomatic relief, and thus the focus should be on three specific categories, namely, the avoidance of allergens, pharmacological treatment and allergen immunotherapy.[4,5]

Allergen avoidance

First-line treatment involves avoiding allergens and irritants.[5] Avoidance strategies may be difficult and/or impractical to implement; however, it effectively improves the management of allergic rhinitis, leading to optimal results when used in combination with pharmacotherapy. Strategies include the avoidance of known or non-specific allergens or irritants that trigger an IgE-mediated response; pollen, dust mites, animals and occupations allergens, as shown in figure 3.[4]

Allergen immunotherapy

Allergen immunotherapy (desensitisation) involves immune-modulating treatment, recommended when pharmacotherapy for allergic rhinitis is ineffective or not well tolerated. Clinical research has established the effectiveness of immunotherapy injections to reduce symptoms, especially in intermittent allergic rhinitis caused by pollen, dust mites, cockroaches and pets. It involves a subcutaneous injection of gradually increasing quantities of the applicable allergen until an effective dose is reached where immunological tolerance is induced.[4,5]

Success rates of up to 90% have been demonstrated for certain allergies. However, it should be reserved for when optimal avoidance measures and pharmacological treatment is insufficient. It's a time-consuming process, with noticeable improvement only showing after 6–12 months, and continuous treatment for up to

Figure 3: Avoidance strategies for allergens and irritants[4]

Pollen	Dust mites	Animals	Occupational	Non-specific
Reduce pollen exposure during the particular season that affects the patient Dry, sunny and windy days have increased pollen counts Keep windows and doors of houses and cars closed if possible Take a shower after outdoor exposure to remove pollen	Cover bedding with impermeable covers Wash covers every 2 weeks in hot water Vacuum clean carpets and rugs if carpeting can't be removed Make use of a dehumidifier and air conditioning	Complete avoidance, although not always practical Alternatively keep animal out of the bedroom and carpeted rooms if possible High-efficiency particulate air (HEPA) filters assist in decreasing cat allergen levels Weekly bathing of pets	Make use of a mask or respirator where needed	Implement reduced exposure or complete avoidance if possible of: Smoke Strong perfumes Fumes Rapid changes in temperature Outdoor pollution

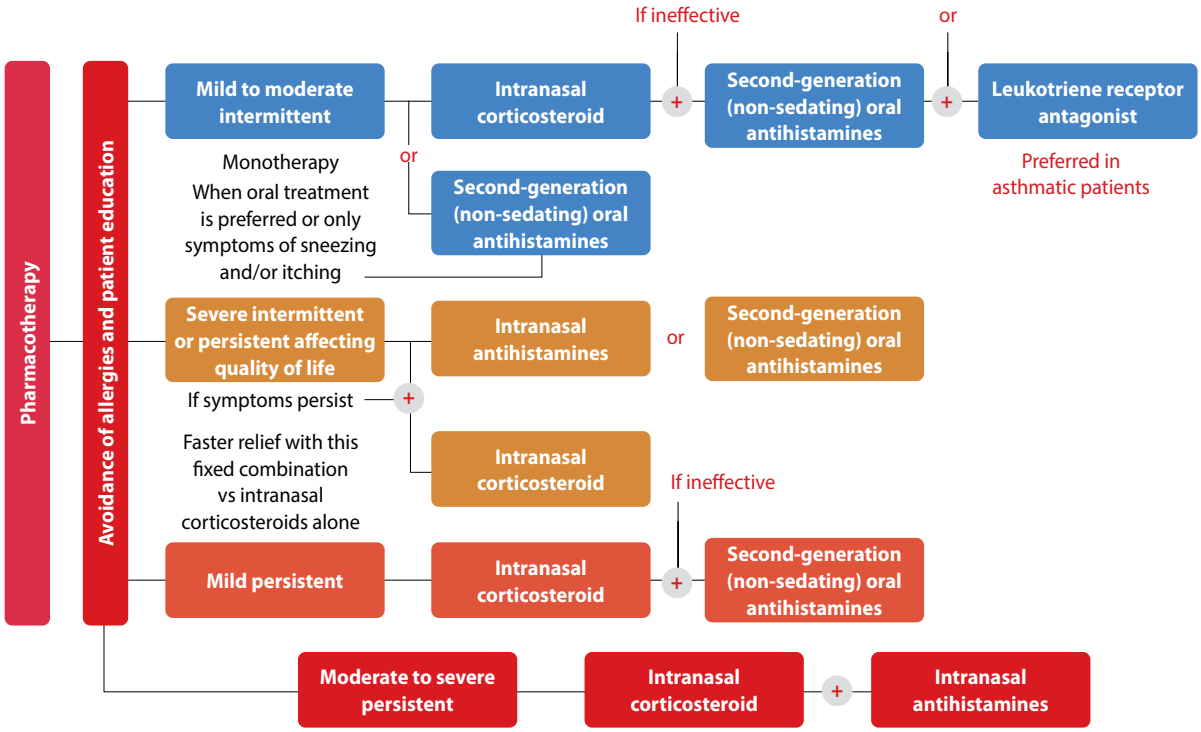


Figure 4: A stepwise algorithm for the pharmacological treatment of allergic rhinitis[8,9]

3–5 years may be required. Treatment involves weekly injections containing incremental increases of the dose over 6–12 months, followed by maintenance doses of the maximum tolerated dose every 3–4 weeks for 3–5 years. Whereafter the beneficial effects can persist for several years.[4,5]

The FDA has approved several emerging sublingual immunotherapies (SLITs) treatment options, consisting of allergen extracts based on the desensitising of patients. It provides a more convenient treatment option than injections, especially in those with specific allergies, but should also be reserved as a last-line treatment option.[5]

Pharmacological treatment

Allergic rhinitis responds well to pharmacotherapy in the majority of patients. Pharmacotherapy options available include oral antihistamines, intranasal corticosteroids and antihistamines, and leukotriene receptor antagonists. Decongestant sprays and oral decongestant therapy may benefit intermittent allergic rhinitis where the treatment required does not exceed five days. Furthermore, ocular antihistamine drops and a short course of oral corticosteroids in severe, acute episodes may provide better relief.[5]

Treatment guidelines recommend monotherapy, in which intranasal glucocorticosteroids remain the gold standard, especially in severe cases and where the quality of life is affected.[6,7] In the case of combination therapy with an intranasal corticosteroid and an oral antihistamine, monotherapy is recommended as the combination does not provide better results than an intranasal corticosteroid alone.

Oral second-generation antihistamines or intranasal antihistamines are, although to a lesser extent compared to intranasal corticosteroids, effective in the symptomatic treatment of allergic rhinitis in mild to moderate cases, with primarily complaints of sneezing and itching, and in those who prefer oral medication.[6,7] Figure 4 provides a treatment algorithm for the pharmacological treatment of allergic rhinitis.

Intranasal corticosteroids

Intranasal corticosteroids are highly effective in treating allergic rhinitis, particularly in patients with severe symptoms and when congestion is reported.[10-12] They exert their effect by preventing the influx of inflammatory mediators and inhibiting the release of cytokines, thereby reducing inflammation of the nasal mucosa.[10,11] Corticosteroids are thus effective in managing symptoms of allergic rhinitis such as itching, rhinorrhea, nasal congestion and sneezing.[10]

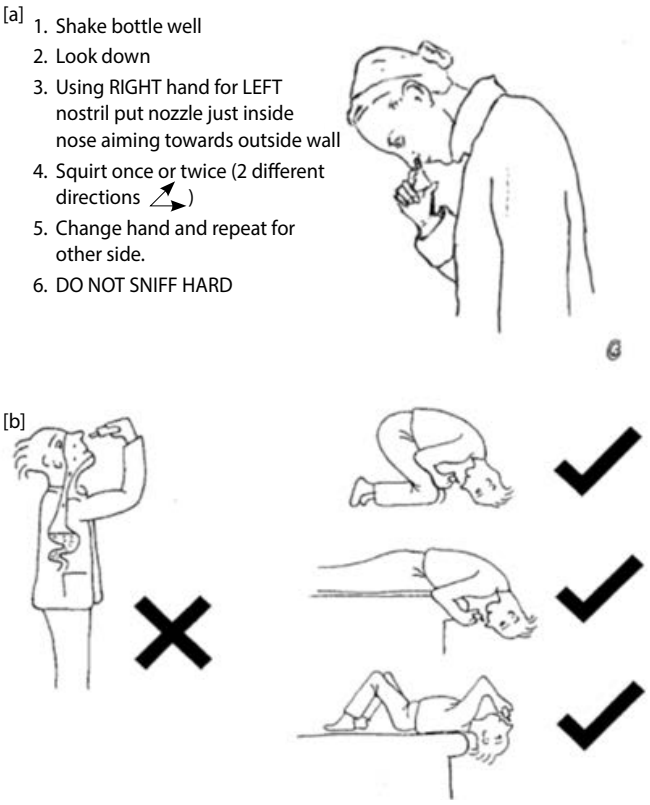
Intranasal corticosteroids are effective as monotherapy; however, they are ineffective against managing ocular symptoms that occur in allergic rhinitis.[12,13] Examples of currently available intranasal corticosteroids include budesonide, beclomethasone, mometasone, fluticasone and ciclesonide (Table II).[11]

Although corticosteroids have a quick onset of action, their peak effect takes several hours or days, and maximum effectiveness is achieved within two to four weeks of use.[12] Local side effects associated with the use of intranasal corticosteroids include nasal dryness, epistaxis and stinging.[8] Long term use of topical corticosteroids can lead to nasal mucosa atrophy, and dosage should be reduced to minimum dose once control of symptoms has been achieved.[8,13]

Table II: Intranasal corticosteroids currently available for the treatment and management of allergic rhinitis [8,10,11]

Intranasal corticosteroid	Mechanism of action	Adults dose (spray)	Minimum age*	Adverse effects
Budesonide	Inhibit the influx of inflammatory mediators Inhibit the release of cytokines	1–2 (32 mcg/spray)/nostril 12–24 hourly (max 4 sprays/24 hours)	6 years	Bitter aftertaste Epistaxis Burning Stinging Headache Nasal dryness Rhinitis medicamentosa Throat irritation
Beclomethasone		1–2 (50 mcg/spray)/nostril 6–12 hourly (max 200 mcg/24 hours per nostril)	12 years	
Ciclesonide		2 (50 mcg/spray)/nostril once (200 mcg/24 hours)	12 years	
Fluticasone furoate		1–2 (27.5 mcg/spray)/nostril 12–24 hourly (max 200 mcg/24 hours per nostril)	2 years	
Fluticasone propionate		2 (50 mcg/spray)/nostril once daily	12 years	
Mometasone		1–2 (50 mcg/spray)/nostril once daily (max 400 mcg/day)	2 years	
Triamcinolone		1–2 (55 mcg/spray)/nostril once daily (max 220 mcg/24 hours)	12 years	

*Minimum age according to South African guidelines, internationally guidelines may differ



Due to the common use of nasal sprays and nasal drops, it is important as a pharmacist to ensure that the patient is educated on the correct use of these dosage forms. Figure 5 illustrates proper usage.

Antihistamines

Following the implementation of allergens and irritants avoidance strategies, second-generation oral antihistamines (desloratadine, fexofenadine, loratadine, cetirizine, levocetirizine and rupatadine) may be used as monotherapy in mild intermittent allergic rhinitis in patients who prefer oral medication or in which the primary complaint is sneezing and itching.[7] Second-generation antihistamines effectively reduce nasal allergic rhinitis symptoms if taken regularly and before exposure to the allergen, without negatively impacting cognitive function as seen in the first-generation antihistamines.[5] Table III shows the recommended dose for adults and paediatric patients.

Table III: Second-generation antihistamines and their recommended dosing[5]

Antihistamine	Adult dosage	Paediatric dosage*
Cetirizine	10 mg once daily	2–6 years: 2.5 mg 12-hourly 6–12 years: 5 mg 12-hourly or 10 mg daily
Levocetirizine	5 mg once daily	2–6 years: 1.25 mg 12-hourly 6–12 years: 5 mg once daily
Desloratadine	5 mg once daily	1–5 years: 1.25 mg daily 6–11 years: 2.5 mg daily
Fexofenadine	120 mg once daily	2–11 years: 30 mg 12-hourly
Loratadine	10 mg once daily	2–12 years < 30 kg: 5 mg once daily > 30 kg: 10 mg once daily
Rupatadine	10 mg once daily	2–11 years 10–25kg: 2.5 mg once daily ≥ 25 kg: 5 mg once daily

*Paediatric dosing according to South African guidelines, internationally guidelines may differ

Intranasal antihistamines

Intranasal antihistamines deliver a rapid, targeted and increased dosage of an antihistamine to the nasal membranes. This treatment option is beneficial even in patients who do not respond to oral therapy. In addition, numerous studies have shown an equality or superiority to oral antihistamines, superiority especially in relieving nasal congestion.[7]

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Leukotriene receptor antagonists

Leukotriene receptor inhibits cysteinyl leukotrienes, a potent inflammatory mediator associated with inflammation, nasal congestion, and mucus production that leads to the development of allergic rhinitis symptoms.[10] Examples of leukotriene receptor antagonists (LTRAs) available include montelukast and zafirlukast. The effectiveness of LTRAs is comparable to that of oral anti-histamines but is less effective than intranasal corticosteroids.[8] Although monotherapy with LTRAs has proven to be effective in reducing SAR, combination therapy can be used to manage patients with severe or persistent symptoms.[10,13] A synergistic effect has been reported between LTRAs and antihistamines in the management of SAR.[13] LTRAs are only recommended as first-line treatment for allergic rhinitis in asthmatic patients as they also act as bronchodilators hence managing both conditions.[8,13] They have an oral admin-istration advantage and are usually well-tolerated with rare cases of headaches, rash and abdominal pain.[14]

Other pharmacotherapy

Decongestants, both oral and intranasal, may provide relief of nasal congestions in allergic rhinitis. However, due to their safety profile, treatment should not exceed 3–5 days. Some of the associated side-effects of oral decongestants include agitation, palpitations, high blood pressure and arrhythmias and therefore should not be used in patients with uncontrolled hypertension or severe coronary artery disease.[5] Prolonged use of intranasal decongestants may result in a rebound nasal congestion (rhinitis medicamentosa). In patients with severe refractory allergic rhinitis, oral corticosteroids have also been shown to be effective.[5]

Conclusion

Allergic rhinitis is non-life-threatening, classified as either intermittent or persistent and further divided into mild or moderate to severe based on several individualised factors. Due to the involvement of multiple ENT organs, complications may arise which may impact quality of life. Management options include avoiding allergens and triggers, pharmacotherapeutic agents, and allergen immunotherapy as a last resort.

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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]

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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.

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Early intervention in acute upper respiratory tract infections

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Foreword

Upper respiratory tract infections (URTIs) are one of the most common diagnoses in the primary care setting across the world,[1] with more than 18.8 billion cases[2] occurring worldwide every year. Most adults will have 2–4 episodes of acute URTI each year, while children have an average of 6–10 episodes.[3-6]

Most URTIs are of short duration and with mild symptoms, but some can lead to serious complications such as pneumonia, rhinosinusitis, otitis media, and exacerbation of asthma and COPD among high-risk individuals. It not only affects an individual's health, but also his/her social life, sleep, school, and/or work performance representing an important burden to society. However, for most URTIs neither cure nor wide-scale prevention through immunisation is yet available – so appropriate treatment requires early intervention. During the pandemic of an acute URTI, early intervention is even more important to prevent viral transmission and infection in susceptible or at-risk populations.

The consensus collated in this paper is an important step to help everyone better understand the impact of URTI and the definition, benefits, and impact of early intervention. This would go a long way towards its advocacy among healthcare professionals as well as the public.

What is early intervention

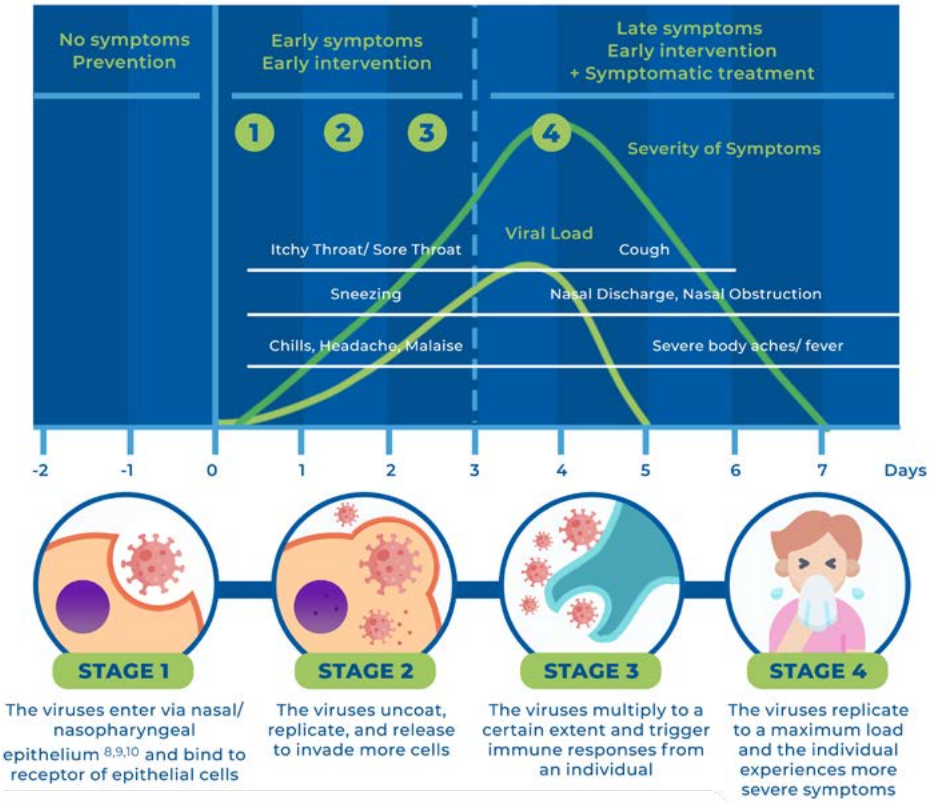
Before defining early intervention, it is critical to understand the life cycle of an acute URTI.

URTIs are mostly caused by viruses and there are over 200 types of respiratory viruses that cause URTIs.[1,3] The development of viral URTIs is largely similar and constitutes four stages. However, there are some variations in duration and symptom manifestation at each stage across different types of URTI viruses.

How does an acute URTI develop?

Early symptoms of acute URTI include sniffling, sneezing, and throat irritation, with occasional chills, headache, and malaise. They can appear anytime within the first 36–48 hours of infection.

Late symptoms include nasal discharge/obstruction, throat pain from inflamed tonsils/adenoids and cough. Chills, headache and



malaise may also occur. These tend to develop over several days and last 1 week or more.

When to intervene?

Stage 1: In absence of symptoms (before)

Those frequently exposed to infected individuals should intervene even in the absence of symptoms when they feel they are at risk of catching an URTI. Intervention at this stage can create a hostile environment for viruses to bind and replicate.

Stage 1, 2 and 3: As early as possible (36 hours)

It is best to intervene as early as possible upon 1st symptom appearance to reduce the chance of developing a full-blown acute URTI. It is easier to slow down or even halt viral replication at the early stages of infection.

- Within 36 hours of 1st symptom appearance.
- Common early symptoms include sniffling, sneezing and throat irritation, with occasional chills, headache and malaises.

Stage 4: After symptoms progress (48 hours)

Intervention may not be as effective in preventing the development of a full-blown URTI or the progression of symptoms once they become disturbing, as viruses have already replicated to a large amount. However, intervening at this stage can still slow down viral replication and minimise spreading to other people.

- ~48 hours to one week of 1st symptom appearance.
- Late symptoms include nasal discharge/obstruction, throat pain from inflamed tonsils/adenoids, and cough. Chills, headache and malaise may also occur at this stage.

"The earlier the better when it comes to early intervention of any infection ... it is like putting a fire out."
R Eccles

"Where there is exposure to the virus; the exposed person may start [using early intervention] as a preventive measure."
A Chua

"Once the viruses replicated in huge numbers and go down to the throat, it will be a bit late ... However, we should intervene at any time to stop viral replication."
DY Wang

Benefits of early intervention

As there is no cure or prevention for acute URTIs, it is important to intervene as early as possible to disrupt the viral replication cycle. There are several benefits of timely and appropriate early intervention in acute URTI.

Reduce chances of developing a full blown acute URTI	Early intervention can slow down and potentially halt viral replication. This may potentially allow the immune system to catch up and eliminate the viruses.
Decrease severity of acute URTI symptoms	Even if a full-blown acute URTI is unavoidable, early intervention can result in shorter or less severe symptoms as it reduces viral load in the infected person.
Reduce viral transmission	Early intervention can reduce breadth of viral transmission by preventing virus particles from reaching their host cells and creating a hostile environment for replication.

High risk groups for acute URTI

URTI is a multi-symptom illness, with symptom profiles varying across individuals in terms of severity, duration, and types.[11,12] However, some people are at higher risk of having a URTI, spreading URTI viruses, or developing more serious URTI complications.[13]

Pre-existing respiratory conditions or smokers

- 80–85% of asthma exacerbations among school-age children are associated with URTI.[11,12]
- URTI is associated with over 50% of COPD exacerbations.[14] The presence of URTI leads to more severe exacerbations, longer recovery times, and can lead to hospitalisation.[14]
- Smoking is a known risk factor for URTI, both for the people who smoke and those around them.

"Patients with asthma or COPD are at high risk ... you will need to intervene as fast as possible to avoid complications."
N Schellack

Children

Children can have 2–4 more URTI episodes than adults per year.[1] While URTI symptoms only persist in 20% of adults at day 10.73% of children still experience symptoms.[15]

"Children often come home from school or daycare with all types of infections and spread them around to the rest of the family."
J Bell

Elderly

Upper and lower respiratory tract infections are the leading causes of death and disability due to infection in the elderly. Compared to the general population, hospitalisation rate for URTI-related pneumonia is 12 times higher for those aged over 75 years.[16]

Immunocompromised individuals

Those with cystic fibrosis, HIV, use of corticosteroids, transplantation, and post-splenectomy are at high risk of developing severe URTI complications such as pneumonia.[13]

Those with frequent contact with infected individuals or high-risk groups

As URTI can easily spread from an infected individual to people around them by contact and airborne transmission,[17] family members of an infected person, healthcare professionals, and adults having frequent contact with infected children can also be at high risk of developing acute URTI.

"As an example – in a household of five, if everyone uses early intervention when one family member caught URTI, four cases can be prevented."
S Salvi

Which early interventions?

Most URTI guideline recommendations focus on treatments that alleviate symptoms such as pain, fever, or inflammation. However, four characteristics[18] of an ideal early intervention include:

- Quick onset of action to tackle rapid viral replication
- Safe to use across the general population
- Effective against a wide variety of pathogens
- Low risk of resistance development against the intervention

Experts also recommend several early interventions, such as mucoadhesive gel nasal sprays and neuraminidase inhibitors. Mucoadhesive gel nasal sprays, in particular, have been gaining more attention from experts in recent years.

What is mucoadhesive gel intranasal spray?

Mucoadhesive gel intranasal spray is a medical device that contains ingredients such as Carbopol, Carrageenan and Hydroxypropyl Methylcellulose (HPMC), and have known physical actions against virus particles in the nose.

The intranasal spray should be used at the first symptom of an emerging acute URTI or upon exposure to URTI viruses.

Mechanism of action

The intranasal spray acts at the back of the nose directly where acute URTI viruses start to bind and replicate. Mucoadhesive gel intranasal sprays can work in the following ways:

1. Trap

Trap the inhaled URTI viruses and cover receptor surface, preventing viruses from reaching their complementary receptors.

2. Slow down

In a formulation with lower pH of 3.5–4.0, it can create a hostile environment for URTI viruses and slow down viral replication.

3. Washout

Have a nasal washout effect to flush out viruses either through nose blowing or swallowing.

Scientific evidence

Several human clinical studies[19-21] indicate that the mucoadhesive gel intranasal spray is effective in reducing URTI duration and symptom severity, and is safe to use.

Forward-looking action

As the most frequently observed infectious disease, acute URTI warrants more attention and proactive management to reduce its burden. We suggest that every individual presenting to a pharmacy/clinic with suspected URTI symptoms, or has comorbid conditions such as a history of asthma/COPD, or has frequent contact with infected individuals should receive a "value brief" on the benefits of early intervention for acute URTI to help pre-empt current and future URTIs.

Effective early intervention

- Reduces chances of the user developing a full-blown acute URTI
- Results in shorter or less severe acute URTI symptoms
- May reduce viral transmission, protecting people around an infected person from contracting a URTI
- Slows down the viral infection rate and may allow the immune system to catch up and eliminate the virus
- Reduces viral replication by preventing virus particles from reaching their host cells and create a hostile environment for replication

When it comes to selecting an appropriate early intervention for acute URTI, mucoadhesive gel intranasal spray fits the requirements as it is effective and well tolerated with a rapid onset of action. Consumer education should focus on when, why and how to use the intranasal spray to effectively fight against acute URTI.

Early intervention guide

WHEN	WHY	HOW
As early as possible upon symptom appearance	Reduce the chance of developing a full blown acute URTI	Apply intervention directly into each nostril

When symptoms are prominent	Decrease duration or severity of symptoms, and minimise viral transmission	Use in combination with symptomatic treatments Administer for at least 2–4 days, and beyond should there be progression of symptoms
In absence of symptoms when being exposed to an infected individual	Prevent virus particles from binding and reduce the chance of developing an URTI	Continue to use until symptoms subside

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Under pressure!

Kaajal Chetty

President, SAAHIP

Kaajal Chetty

It's the terror of knowing what this world is about, the dread of knowing what is expected of us, the trepidation of knowing that deadlines must be met. The pharmacist of today is certainly under pressure!

Whether you work in the private or public sector, your journey to providing quality healthcare to your patient can sometimes feel overwhelming. Pharmacists face many challenges in their day-to-day operations. Disparate resources, time restraints, stock outages, communication breakdown between management and staff, out-dated information or even information overload are examples of such challenges.

Resilience and innovation seem to be pre-requisite qualities for pharmacists that we summon to overcome the barriers to effective pharmacy practice. We are often subjected to sub-standard conditions. And yet we make it work. We achieve the impossible with the little that we have and the price to pay is our job satisfaction. Perhaps it is because we truly care for people and their well-being or because we honour the Oath that we have taken? Is this a healthy perspective for the pharmacist? Do these pressures pushing down on us, not affect our mental, emotional and physical well-being? Remember the sayings, "In order to care for others, you must care for yourself first.""You can't pour from an empty cup, take care of yourself first."

In order for us to provide that quality service to our patients, let us firstly focus on ourselves and our practices before we move on to the next task. Let us try to find solutions to existing problems rather than ignore issues and potentially create bigger dilemmas. We need to put in the effort of creating a healthy working environment that is essentially safe for the pharmacist, support staff and patient. Work with your management to create the setting you need to function at your optimum. Whilst we trust that it is in the capable hands of management that all solutions lie, ideas from the floor may be more practical and easier to adopt. So, go on, share those ideas on how you can improve your surroundings. Once your house (pharmacy) is in order, unpacking the bigger issues may be easier.

We are the multi-tasking medicine experts, the pharmacists that can handle multiple matters concurrently. Is this an unrealistic expectation? Is this an unnecessary pressure? Unfortunately, our profession is entwined with many clinical and non-clinical issues that require our attention. Antimicrobial Resistance, Drug-Resistant Tuberculosis and Ideal Hospital/Clinic are a few topics that may need daily attention aside from your regular duties.

Familiarise yourself with available policies on the subject matters. Use reliable information sources. Include your interns in summarising and disseminating the information to support staff. These essential matters require attention by all categories. Share the task where you can. Teamwork can produce excellent results.

Rosters, to-do lists and a diary can be just the right amount of magic that you need to help get your 25-hour day organised (especially with multi-coloured pens!).

A saline flush or steam may help relieve another form of pressure but remember self-care is necessary to help you de-stress.

It is only fair to mention the pressure felt by the qualified pharmacist who struggles to find permanent employment. With all the healthcare transformation that the country is going through, with the unspoken promise that the need for the pharmacist's expertise will be of greater demand, I do hope that you find your place in this ideal picture.

It's the hope and faith of knowing what this world could be someday that drives us to do better, to not give up. You've got this! Diamonds are created under pressure.

Rational use of medicine in tuberculosis patients presenting with adverse effects

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Runner-up in the Life Healthcare Award for best presentation at the SAAHIP Conference 2022

Introduction

Erin M Watt

Tuberculosis (TB) is one of the leading causes of death globally, despite being curable and partially preventable. Some of the most important barriers to successfully treating TB infections are the development of drug resistance and the presentation of adverse drug reactions (ADRs).[1]

The prevalence of multidrug resistant (MDR) and extensively drug resistant (XDR) organisms can be minimised through the rational prescribing and use of TB treatment. By ensuring that the correct medication is prescribed at the correct dose based on the patient's profile, drug resistance can be prevented. Patient non-adherence also contributes to the increased risk for both MDR and XDR TB, although both can be acquired as primary infections.[2]

Adverse drug reactions may occur in as many as 85% of patients on first-line treatment and 96% of patients on second-line treatment.[3] An adverse drug reaction is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[4] In the event of an ADR, appropriate clinical management can limit harm to the patient and minimise the risk of inadequate therapeutic levels for the identified infection.

Pharmacists have extensive knowledge regarding medication and can play a significant role in the detection, identification and prevention of ADRs. They can also contribute to the rational use of TB medication in ensuring both appropriate use and advising on the appropriate management of ADRs. Evidence-based medicine (EBM) may be used to promote rational medicine use. EBM is the intentional and rational use of current and relevant evidence in decision-making regarding individualised patient care.[5] The EBM cycle can be used by pharmacists to identify the most appropriate literature to answer an identified clinical question and therefore manage a patient-focused query (as depicted in Figure 1).[6]

Figure 1: Evidence-based medicine cycle[7]

Case presentation

The clinical case was encountered at a public sector district hospital in the Western Cape. The case highlights the role of the pharmacist, as part of the healthcare team, in the optimisation of TB treatment in patients with complications.

Patient presentation

The patient was a 37-year-old female with a body mass index (BMI) of 19kg/m^2. Her past medical history included being diagnosed as HIV-positive, with a CD4 count of 53 cells/ul, and drug-sensitive pulmonary TB. At the time of her TB diagnosis, the patient was initiated on the first-line regimen using the fixed-dose combination of rifampicin (150mg), isoniazid (75mg), pyrazinamide (400mg), and ethambutol (275mg) (R/H/Z/E). The patient was not receiving antiretroviral treatment (ART) and was initiated on cotrimoxazole for the prevention of opportunistic infections. The patient subsequently presented with a skin rash, which was diagnosed as Stevens-Johnson syndrome (SJS), and she was switched to a regimen of linezolid, levofloxacin and terizidone. The patient was referred from the local clinic with reports of extreme anxiety and fear that presented following the change in her TB medication therapy. After assessment of the patient, a diagnosis of terizidone-induced psychosis was made. A medication-related problem was identified as the patient required alternative treatment of active TB until it was safe to rechallenge with the standard first-line TB treatment regimen (R/H/Z/E).

Tuberculosis

Tuberculosis (TB) is an infectious disease caused by the organism *Mycobacterium tuberculosis (M.tb)*. This disease continues to be one of the leading causes of death in South Africa, with an estimated 58 000 deaths due to TB infection in 2019 and is therefore of great importance to the healthcare system.[1]

If droplets containing the TB bacterium are inhaled, they can enter the respiratory airways and be carried to the alveolar spaces. As a

part of the immune response, the bacilli are engulfed by alveolar macrophages and most of the bacterial cells are either inhibited or destroyed. However, due to the lipid-dense bacterial cell wall, some bacilli may survive and continue to grow within the macrophages. This can lead to an active infection and eventually cause extensive damage to the lung tissue and ultimately death.[8]

Drug-sensitive TB is defined as an infection which does not demonstrate resistance to any of the first-line TB medications. According to the South African standard treatment guidelines, first-line treatment for drug-sensitive pulmonary TB consists of a total of six months treatment with antimycobacterials. An intensive phase of two months of treatment with R/H/Z/E, dosed according to the patient's weight, is followed by four months of continuation phase treatment using only rifampicin and isoniazid (R/H), dosed accordingly (Table I).[9] The goal of treatment is to complete the full course of treatment, eradicating the infection, with minimal presentation of adverse effects. Adverse effects may hinder adherence or prevent full completion of treatment.

Table I: TB regimen for adults and children older than 8 years weighing more than 30kg[10]

Pre-treatment body weight (kg)	Intensive phase	Continuation phase	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
30–37	2 tablets	2 tablets	
38–54	3 tablets	3 tablets	
55–70	4 tablets		2 tablets
> 70	5 tablets		2 tablets

The first-line regimen is known to produce a host of adverse effects, many which are predictable and manageable. However, some severe reactions may require discontinuation of treatment. The current recommendation is to stop the offending TB medication when adverse effects are detected and to consider rechallenging once the identified ADR has been resolved.[11]

Clinical dilemma

The patient presented with acute-onset psychosis secondary to terizidone use and therefore the patient's therapy required adjustment. In such cases, the offending agent should be discontinued and replaced with an appropriate alternative. On admission to the hospital, the patient's prescribed medication was reviewed by the ward pharmacist. The following medication-related problem was identified:

1. The patient required alternative drug therapy with a background TB regimen until it was possible/safe to rechallenge with R/H/Z/E.

In order to elicit the most appropriate and up-to-date information, an evidence-based approach was applied to resolve this problem. Through this process it was found that the most appropriate background regimen for the treatment of TB in the presence of ADRs consists of any three agents therapeutically active against *Mycobacterium tuberculosis*.[12] As the background regimen is administered in conjunction with first-line TB medications during rechallenge, it is recommended to select agents with short half-lives to minimise the unnecessary exposure of the body to multiple medications. Therefore, the pharmacokinetics of these agents should also be considered in the selection of the most appropriate background regimen.

Based on the patient's profile and the available agents it was recommended to initiate the patient on linezolid, levofloxacin, and amikacin until rechallenge could take place. The patient's medication-related problem was thus resolved, and the medication therapy was optimised through discussions between the pharmacist and the medical team.

Patient outcome

While the patient was in hospital, the first-line TB treatment was re-introduced, using the fixed-dose combination, and no further adverse effects were observed. Cotrimoxazole was identified as the probable cause of the Stevens-Johnson syndrome and was not re-initiated. It was noted that the options for prophylaxis of opportunistic infections were to be reviewed at follow-up, two weeks post-discharge, when the initiation of ART was also to be reviewed.

Lessons learnt

This case highlighted the importance of rational medicine use in the management of TB, the associated adverse effects and the role it can have in the prevention of resistance. The effectiveness of EBM in the management of complicated patients was also demonstrated. In this scenario, through the application of EBM principles, the healthcare team was able to identify the most appropriate TB regimen for this patient. This process was led by the pharmacist, demonstrating the value that a pharmacist can add as an active member of the healthcare team at ward level. Pharmacists can optimise patient health outcomes by providing pharmaceutical care and ensuring rational medicine use.

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