July/August 2025. Vol 92 No 4
SA Pharmaceutical Journal

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ISSN: 2221-5875

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SA Pharmaceutical Journal

Official journal of the

Pharmaceutical Society of SA
incorporating
- Academy of Pharmaceutical Sciences
- South African Association of Community Pharmacist Sector of the PSSA
- SA Association of Hospital and Institutional Pharmacists
- SA Association of Pharmacists in Industry

www.sapj.co.za

ISSN: 2221-5875

ADVERTISING SALES
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SUBSCRIPTION
info@medpharm.co.za

PUBLISHER
The Pharmaceutical Society of South Africa in collaboration with
Medical & Pharmaceutical Publications (Pty) Ltd
trading as Medpharm Publications
Registration No 93/0794007

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Medpharm Publications

Medpharm Publications,
Ground Floor, Centurion Wine & Art Centre,
123 Amkor Road, Lyttelton Manor
PO Box 14804, Lyttelton, 0157
Tel: (012) 664-7460, Fax: (012) 664-6276
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S Afr Pharm J 2025 Volume 92 Number 4 (July/August)

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SAPJ Author Guidelines

Thank you for choosing SAPJ in which to publish your paper.

Aims, scope and review policy

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.

Papers dealing with medicines safety issues, including the safe and appropriate prescription, administration and use of medication as well as pharmacovigilance, are strongly advocated in SAPJ. SAPJ further supports pharmacists in transforming the pharmacy into an accessible, basic primary health care facility for preventing and treating primary health care conditions through diagnosis, screening and treatment.

The journal is currently indexed by Google Scholar via www.sapj.co.za and enjoys wide international exposure. An 'electronic long, paper short' policy will be followed for original papers where abstracts of original papers are featured in the printed copy with the full version available online.

Online submission

All articles must now be submitted online at www.sapj.co.za

The electronic submission process will prompt you to check off the following declarations:

1. This manuscript has currently only been submitted to SAPJ and has not been published previously.
2. This work is original and all third party contributions (images, ideas and results) have been duly attributed to the originator(s).
3. Permission to publish licensed material (tables, figures, graphs) has been obtained and the letter of approval and proof of payment for royalties have been submitted as supplementary files.
4. The submitting/corresponding author is duly authorised to herewith assign copyright to Medical and Pharmaceutical Publications (Pty) Ltd
5. All co-authors have made significant contributions to the manuscript to qualify as co-authors.
6. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
7. A conflict of interest statement has been included where appropriate.
8. A title page has been uploaded as a separate supplementary file and the submission adheres to the instructions to authors in terms of all technical aspects of the manuscript.

How to submit your paper online:

1. Visit www.sapj.co.za.
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3. Select Author.
4. Click on CLICK HERE TO FOLLOW THE FIVE STEPS TO SUBMIT YOUR MANUSCRIPT .
5. Follow the five steps to submit your paper.

Article sections and length

The following contributions are accepted (word counts include abstracts, tables and references):

Original research:	3 200–4 000 words
Evidence- based pharmacy practice:	3 200–4 000 words
Reviews:	2 400–3 200 words
Case studies:	1 800 words
Scientific letters:	1 200–1 800 words
Letters to the editor:	400–800 words

For a full version of the SAPJ author guidelines, please visit www.sapj.co.za

A place at the table: why SAPJ's accreditation matters for pharmacy in South Africa and Africa

There are moments in the life of a profession when the present suddenly stretches backwards into history and forward into possibility — when the labour of many years is acknowledged, and a door swings open to a new future. The recent confirmation of the *South African Pharmaceutical Journal* (SAPJ) on the Department of Higher Education and Training's (DHET) accredited Scopus list is such a moment.

For nearly a century, since its first publication in 1931, SAPJ has chronicled the pulse of pharmacy in South Africa — its science, its policy debates, its ethical dilemmas, its evolving practice. Yet, recognition on the DHET list gives this century-old voice not only legitimacy in local scholarship but also visibility in the global conversation.

Like a baobab tree whose roots run deep and wide, SAPJ stands not alone but because of all who have tended, watered, and protected it over generations. Its strength is the community's strength, and this recognition is a fruit borne of many hands and hearts. In the spirit of Ubuntu, the journal flourishes because our profession has flourished—each article, each review, a testament that *"a person is a person because of other people"*.

Why this accreditation matters?

Inclusion on the DHET list means that peer-reviewed articles published in the SAPJ now "count" in academic terms: universities can claim research subsidies for contributions here. This has immediate and very concrete implications:

- **For pharmacists and other scientists in academia**, it offers a trusted, local platform to publish work that is recognised by South Africa's higher education funding system, easing the tension between publishing abroad for subsidy and publishing at home for relevance.
- **Practicing pharmacists outside academia:** Accreditation means that real-world innovations, case reports, and practice-based insights from pharmacists in hospitals, clinics, and community pharmacies can now be published and acknowledged. Your work—improving patient care, managing medicines, optimising workflows—can now shape the international, national and regional understanding of pharmacy practice, not just remaining informal knowledge at your workplace. Elevating the possibility of practice-led research and innovation being disseminated through a formally accredited channel, ensuring that community pharmacy, industry-driven discoveries, and clinical interventions are not overlooked.

In short, SAPJ's accreditation dismantles the old divide between scholarship and practice. Where once our pharmacists felt like outliers to the broader academic system, we now have not just a seat at the table but a platform shaped by us — rooted in Africa, speaking to the world.

This recognition also carries a symbolic weight beyond our borders. Africa has historically been underrepresented in global pharmaceutical publishing. The continent's problems and solutions are often studied elsewhere, written about elsewhere, published elsewhere.

Like a pharmacist carefully measuring and compounding, this editorial achievement reminds us of the alchemy between rigour and relevance. We are not merely importing knowledge but producing it; not simply imitating global science but shaping it.

Where SAPJ fits in the continental landscape

Here, the broader picture deserves attention. Currently, recognised and accredited pharmacy-related journals in South Africa and Africa are rare.

In South Africa, the SAPJ is now accredited by DHET (through the Scopus list). There have historically been few other pharmacy discipline-specific accredited journals. Outside of SAPJ, much South African pharmacy research has been pushed into broader medical journals or international outlets. In Africa as a whole, accredited and indexed pharmacy journals are limited. Examples include the *African Journal of Pharmacy and Pharmacology* (Nigeria, widely indexed), the *East and Central African Journal of Pharmaceutical Sciences* (Kenya/Uganda), and the *Journal of Pharmaceutical Policy and Practice* (though international, it hosts significant African scholarship). However, very few of these carry DHET recognition within South Africa's subsidy system.

What this means is that SAPJ is carrying a disproportionate responsibility and opportunity — it is the primary accredited, local journal fully dedicated to pharmacy in South Africa, and one of only a handful across the continent that blends discipline specificity, accreditation, and continental identity.

The metaphor of compounding

Pharmacy is, in its essence, the art of compounding: taking disparate ingredients and producing something unified, effective, and life-giving. This accreditation is much the same. It required years of

investment from the societal (PSSA), editorial (SAPJ), and publishing house (Medpharm) leadership, an editorial board representing South Africa's leading universities, and the consistent scholarly contributions of pharmacists in every field. It was not the achievement of one person, but of an entire profession working slowly, deliberately, like careful compounding — validating the old truth that the best remedies arise not from haste, but from craft.

Yet accreditation is not the end of the story. It is, in fact, only the license to begin a new chapter. With visibility comes responsibility:

- To ensure that SAPJ remains rigorous in peer review, uncompromising in ethics, and fastidious in quality.
- To invite the private sector pharmacist, the hospital pharmacist, the community-based practitioner into these pages as much as the academic scientist.
- To make room for the contested questions — around policy, equity, cost, accessibility — the issues that define pharmacy in the African context.

Like the pharmacist on a midnight shift, SAPJ must remain vigilant: steady hands, clear eyes, and a deep awareness that what it dispenses is not just knowledge but trust.

This accreditation is more than a bureaucratic milestone. It is a profession saying to itself — and to the world — *"we are here, we have something to say, and our scholarship is worthy".* For the next generation of pharmacists, it means they can train their academic voice at home, with confidence that their work will resonate both locally and globally.

For South Africa and Africa, it means the pharmacist finally has a journal that not only serves the profession but also serves the academic ecosystem — binding together practice, science, and policy in our own context.

Sometimes, achievements are loud — trumpeted and celebrated. Sometimes, they are quiet, like a carefully prepared dose that will, over time, change the course of health. The accreditation of SAPJ is both: a shout of recognition, and a quiet assurance that pharmacy in South-Africa is stepping into its rightful place in the global literature of medicine.

Warm wishes

Natalie Schellack

The external and internal dynamics within and outside the Pharmaceutical Society of South Africa in its growth path

Tshifhiwa Rabali
PSSA President

As we have all witnessed the growth in membership of the PSSA in recent years, we can also expect to see the changes and dynamics that naturally accompany such growth. Like all societies and organisations, the Pharmaceutical Society is a living entity—and it is not exempt from the realities that come with changes and development.

I will break down the realities of the visible involvement emerging within the PSSA by examining its various structures, i.e. branches, sectors, the Young Pharmacists' Group, SAPSF, and other stakeholders.

Branches are the pillars of any organisation—they are where growth truly begins. This includes all branches of the PSSA, along with its various sectors. As the backbone of a living organism like the PSSA, branches play a critical role in sustaining momentum. With a few exceptions, we've seen significant changes in leadership at branch level in recent years. This transition has sparked renewed interest among pharmacists across the country to engage with and belong to the PSSA, ultimately driving the Society's growth.

The initiative to revive inactive branches, which began 16 months ago, is progressing well and continues to generate strong interest from members of the PSSA affiliated with those branches. While a few branches still require support to ensure their sustainability and continued service to their members, the response so far has been encouraging. I must acknowledge and appreciate the warm and welcoming reception we have received from the branches we have already visited—they have been both accommodating and enthusiastic.

Branch leaders must recognise that members residing or working within the jurisdiction of a branch are often active and engaged in their own right. As the PSSA, we are guided by their experiences and perspectives when assessing the progress—or challenges—within a branch. We are committed to listening to our members, and when issues arise, we will engage openly with both branch leadership and the concerned members to find constructive solutions.

As more pharmacists—especially young pharmacists—continue to join the PSSA, we are seeing a growing trend of involvement and an increase in questions asking what the branch or PSSA is doing for its members. On a positive note, many branches are actively serving their members, with annual AGMs held regularly and officials elected to their positions. To these branches I say: Well done.

Sectors are the four pillars of the PSSA, and through the unity we share, the PSSA continues to grow its membership year after year. Sectors play a vital role within the PSSA, and the ongoing involvement and enthusiasm of members across all sectors have not gone unnoticed. The increasing interest in leadership roles is especially commendable. In the past, some sectors have held conferences and gatherings without involving PSSA leaders, but this must change. The Presidential Committee of the Pharmaceutical Society of South Africa looks forward to participating in these events, providing members with the opportunity to learn about the current initiatives and benefits of their PSSA membership.

The Young Pharmacists' Group (YPG) is vital to the continued survival and growth of the PSSA, as they represent our future leaders. When the PSSA adopted the YPG concept from FIP ten years ago, it was with the clear purpose of nurturing future leadership and making succession planning a daily reality. The YPG has brought tremendous activism to the PSSA's structures and has grown significantly over the past decade, with representation in nearly every PSSA branch across the country. As leaders, it is essential that we listen attentively to their constructive contributions, as this will ultimately benefit the entire Society.

We have seen growing interest from the South African Pharmaceutical Students' Federation (SAPSF) since the PSSA embraced them as a stakeholder. While this progress brings its own challenges—requiring us to provide ongoing guidance—I am optimistic about the students' future within the PSSA. It is important that we all encourage them to maintain consistency and professionalism in their public statements and actions, as this helps preserve the valuable relationships we have built with other stakeholders.

Lastly, I would like to sincerely thank the Presco members who volunteered to be part of the delegation visiting the branches. We remain committed to continuing the work that benefits the PSSA, ensuring that its mandate is fulfilled for the benefit of all its members—including pharmacists, pharmacy students, pharmacist's assistants, technicians, and all other pharmacy personnel.

Thank you

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Breakthrough Inhalation Therapy: Harnessing the Power of Silver for Respiratory Health

During the height of the COVID-19 pandemic, doctors around the world searched desperately for therapies to ease suffering and save lives. In Zimbabwe, where hospitals had limited resources, frontline healthcare workers turned to an innovative and cost-effective treatment: inhaled pharmaceutical-grade ionic (Ag^+) silver. The results were striking. Patients showed improvements that rivalled, and in some cases exceeded, those seen in better-equipped facilities in the developed world.

This unexpected success has drawn attention to Silverlab Healthcare, a South African company pioneering a safe, research-backed inhalation therapy that could change how we manage respiratory infections.

Why Silver?

Silver has long been recognised for its antimicrobial properties. Today, advanced formulations of ionic (Ag^+) silver are making it possible to apply this ancient remedy in cutting-edge ways.

A. Superior Absorption

The lungs are home to 300 million alveoli – providing a mucous membrane surface area as large as a tennis court. This means that inhaled medicines can be absorbed almost as efficiently as intravenous treatments, offering rapid relief where it's needed most.

B. Proven Safety

Silverlab's inhaled ionic silver has been rigorously tested in cell, animal, and human studies. While the typical inhalation strength is 18 parts per million (PPM), research conducted by Silverlab has shown that concentrations up to 450 PPM remain safe when produced in a pharmaceutical-grade, GMP-certified facility.

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Beyond COVID-19, ionic silver demonstrates activity against a wide range of respiratory viruses and bacteria. Silverlab Healthcare is the only silver manufacturer conducting ongoing research into its medicinal applications, placing it at the forefront of this medical breakthrough.

How to Use Silverlab Nebulising Liquid

- Nebulise 5 mL, 2–3 times per day during illness, using a standard nebuliser (no saline dilution needed).
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What Sets Silverlab Apart?

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A Vision for the Future

Respiratory infections remain one of the world's greatest health challenges. By uniting ancient wisdom with modern science, Silverlab Healthcare is offering doctors and patients a safer, smarter, and more effective tool for protecting respiratory health.

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Available at all major pharmacies.

More info

Reflecting on the PSSA Strategic Plan (2025–2030)

As the PSSA began this journey to develop our new strategic plan, we did not start with documents or templates. We started by observing and listening. We listened to the concerns whispered in webinars, voiced in branch meetings, and one-on-one conversations. We asked ourselves: What do our members need to thrive? What does the pharmacy profession need to evolve and lead in a changing health system? The process that led to this strategy was inclusive and introspective. It was driven by a realisation that, to be the undisputed guardian and leader of the profession, the PSSA would need to stay relevant, connected, and responsive in a changing professional and national landscape.

The strategic planning process began with a comprehensive consultation, most notably through a member survey that posed challenging yet necessary questions: What are the most critical issues in pharmacy? Where is the PSSA falling short? What should the next few years look like? We viewed the survey responses as a call to action as they revealed an organisation struggling with low visibility, internal fragmentation, regulatory pressure, and a sense of disconnection among members, including pharmacists outside the PSSA's formal membership. These issues became the foundation of a new strategic direction, which forced us to confront outdated assumptions and imagine new ways of working, thereby becoming more relevant, responsive, member-centred, and accountable.

What emerged was a strategy structured around four objectives: increasing member engagement, enhancing visibility, optimising resources, and strengthening professional advocacy. The strategy is supported by a mission that supports and promotes the profession in advancing patient care and ensuring access to medicine for all by upholding professional standards of pharmaceutical practice in all settings. It is guided by our values, which underscore our commitment to uphold professional integrity and accountability in all our actions, ensuring transparency and responsibility in everything we do. Through collaboration, we strive for excellence while advocating for the needs of those we serve, always working together to create a positive, lasting impact.

The first strategic objective aims to transform passive membership into active engagement by encouraging networking, leadership development, and inclusive communication. It embraces the diversity of the pharmacy profession across demographics and practice areas by knowingly including pharmacy support personnel and underrepresented sectors. The second strategic objective prioritises visibility as a tool for influence, positioning the PSSA and pharmacy to shape public perception and to highlight the intrinsic contribution of the pharmacy profession in delivering effective healthcare in South Africa. Through various media, digital platforms, and strategic campaigns that elevate pharmacists' contributions to healthcare, this objective aims to strengthen advocacy, build public trust, and attract future pharmacy professionals.

The third strategic objective redefines resource optimisation by seeking to harness the underutilised potential of members, strengthen financial governance across branches, and engage external partnerships for sustainability. In doing so, we are transforming resource challenges into opportunities for collaboration and innovation. The fourth strategic objective repositions the PSSA as a proactive, credible voice in health policy through evidence-based advocacy and sustained relationships with policymakers. It emphasises that meaningful representation must be earned through consistent relevance, trust, and strategic engagement.

The strategic plan also emphasises stakeholder mapping as a crucial step and a strategy for alignment. Each stakeholder's interests were considered, and actions were proposed that aligned professional goals with national health outcomes. The mapping served as a reminder to the Society that effective advocacy and sustainable reform require more than mere internal alignment, but also a coordinated action with and through diverse stakeholders.

The PSSA 2025–2030 Strategic Plan is more than a forward-looking document; it is an indication that we are paying attention, that we are willing to adapt, and that we are committed to walking this path together. This new plan reflects our commitment to inclusivity, innovation, and professional excellence. More importantly, it reflects the voices of our members that shaped it and the needs of our members that inspired it.

Its success will depend on our willingness to continue listening, learning, and building a profession that serves patients, advances science, and uplifts every pharmacist. We hope it will be viewed as a renewed social contract between the Society and its members, as well as between the profession and the public it serves. Therefore, we invite our members not only to be recipients of this strategy but also to be co-designers of a future where pharmacy stands tall, respected, and indispensable in every corner of our healthcare system.

The PSSA/Alpha Pharm distance learning programme 2025

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 3, 2025 – Sexually transmitted infections

According to the World Health Organization (WHO), sexually transmitted infections (STIs) continue to affect millions of people worldwide. It is estimated that over 376 million men and women aged 15–49 years are infected with one of the four common STIs—chlamydia, gonorrhoea, syphilis, or trichomoniasis. This translates to an average of more than one million new infections every day worldwide.

While some STIs can also be transmitted through non-sexual routes—such as from mother to child during childbirth or through contaminated blood—the focus of this module is specifically on STIs acquired through sexual contact. This module provides an overview of the more common STIs (chlamydia, gonorrhoea, syphilis, trichomoniasis, herpes, human papillomavirus and hepatitis B), their symptoms and treatment, with a focus on syndromic management, which is used in South African primary healthcare settings. It addresses the types of STIs, risk factors, diagnostic methods, pharmacologic management and preventative measures. It also highlights the pharmacist's role in supporting patients and promoting safe sexual practices.

Human immunodeficiency virus (HIV) is a major STI in South Africa. However, its complexity requires separate, focused coverage and is therefore not included in this module.

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 2025 for pharmacy staff

The PSSA/Alpha Pharm pharmacy staff clinical education programme continues to offer front-shop assistants or pharmacists' 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 3, 2025 – Sexually transmitted infections

A sexually transmitted infection (STI) is an infection transmitted through blood, semen, vaginal fluids, or other bodily fluids during sexual contact (oral, anal, or genital) with an infected partner.

STIs can affect anyone who is sexually active. STIs are therefore common, affecting millions of people worldwide. On average, there are more than one million new sexually transmitted infections happening every day worldwide.

South Africa has one of the highest rates of STIs (including HIV) in the world. Sexual assault further increases the rate of STIs in South Africa, as survivors are often exposed to unprotected sex and injuries that raise the chance of acquiring a sexually transmitted infection.

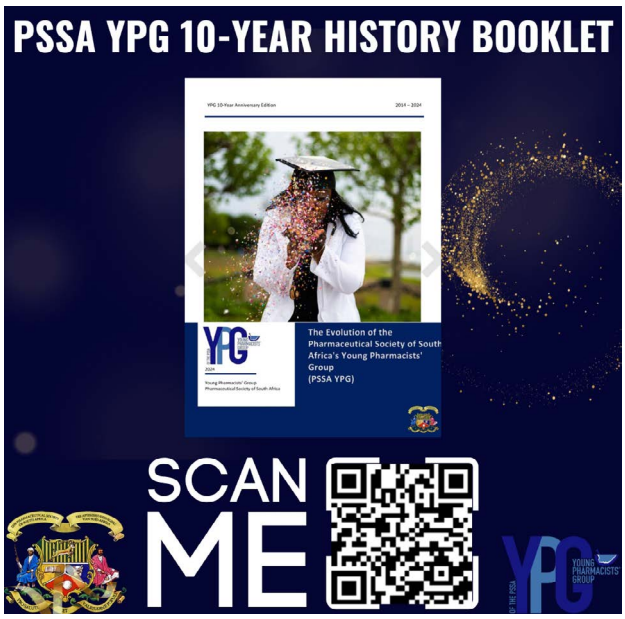
Human immunodeficiency virus (HIV) is a major STI in South Africa. However, it is a complex infection that requires separate, focused coverage and is therefore not included in this module.

This module provides an overview of STIs, including the more common types, how they are spread, factors that increase their spread, common symptoms, possible complications and how they are treated and can be prevented.

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.

PSSA YPG: Let's Catch Up!

Last year, the PSSA YPG celebrated 10-years of existence. It has been a long journey of building, chopping and changing but ultimately a unified mission of promoting the goals of PSSA by encouraging the young members of PSSA to participate in PSSA projects and activities. The milestone was marked by two launches of the PSSA YPG 10-year History booklet, one that took place at the historical 82nd International Pharmaceutical Federation (FIP) World Congress in Cape Town, South Africa and another that took place at the PSSA National office in Lynwood Pretoria on 11 November 2024. If you have not come across the recollection of the achievements and activities of the YPG, scan the QR code below or click here to access the 48-page digital booklet



PSSA YPG History Booklet

PSSA History Book Celebration Event

So what has the Steering Committee been up to since then?

1. Attending the SAAHIP Limpopo branch "I Care for Eye Care" conference and AGM

This conference was well attended by many young pharmacists and pharmacy students and emphasised the need for pharmacists to pay closer attention to the vital organ that enables vision and can have detrimental effects on the quality of life if neglected. Kevin Baloyi was in attendance alongside Ntombizodwa Luwaca who delivered a presentation on Diabetic Retinopathy.

Left to right: K Baloyi, K Letuku, N Mafarafara, N Luwaca

2. Attending the SAAHIP Mpumalanga branch conference and AGM

Kevin Baloyi attended this intriguing and thought-provoking conference and delivered a presentation titled "The digital revolution in Pharmacy."

3. Attending the SAPSF Conference Gala Dinner

Ntombizodwa Luwaca attended the SAPSF conference Gala dinner which took place in Gqeberha on Saturday 1 February 2025. This was an evening filled with many of the pharmacy students' achievements in 2024. The PSSA YPG witnessed the launch of the second publication of SAPSF and enjoyed a night of celebration with the future of pharmacy and those that have mentored and guided their paths. Alice Lategan from PSSA Cape Midlands, lecturers from Nelson Mandela University and the PSSA Executive Director Refiloe Mogale were also in attendance.

4. PSSA YPG at the CIPC IP Youth Awards

Kevin Baloyi attended this evening function that celebrated the achievements of youth of South Africa.

5. PSSA YPG at the SAPHEX symposium

Ntombizodwa Luwaca attended the SAPHEX Pharmaceutical Indaba which was organised by the PSSA to initiate dialogue on pharmacy human resources in South Africa. She delivered a presentation titled "Yini Indaba" which outlined the results of the PSSA YPG unemployment survey. This presentation was thought-provoking and provided some statistics on the ongoing unemployment crisis among South African youth which is currently affecting young pharmacists. The Pharmaceutical Indaba was recorded and is accessible here.

6. PSSA YPG at the National SAAHIP Conference and AGM

Anele Khwela, Kevin Baloyi, and Ntombizodwa Luwaca attended this conference and AGM at the Champagne Sports Resort in Drakensburg, Kwa-Zulu Natal. Subcommittee members Aisha Adams, Matladi Stanley Morapedi, and Sharon Phiri were also in attendance. This conference provided an excellent platform for young pharmacists to network, enhance their knowledge, and of course have plenty of fun! The conference focused on the future of pharmacy 5.0 with the integration of digital technologies to enhance the practice of pharmacy. Ntombizodwa delivered a presentation on the PSSA YPG's current structure and the results of the unemployment survey, similar to those presented at the Pharmaceutical Indaba.

Where can you find the PSSA YPG next?

The PSSA YPG is committed to bringing young pharmacists closer to opportunities that will foster their growth and contribution to the advancement of the pharmacy profession. The mentorship programme, professional and innovation project are two dynamic projects that will soon be available to young pharmacists nationwide and we encourage full participation to reap the benefits of these programmes. There are also many networking opportunities available this coming year:

1. **PSSA South African Association of Pharmacists in Industry conference**
   Date: 4–6 June 2025
   Venue: CSIR International Convention Centre, Pretoria, Gauteng
2. **PSSA Academy of Pharmaceutical Sciences conference**
   Date: 31 August–2 September 2025
   Venue: Lagoon Beach Hotel, Cape Town, Western Cape
3. **PSSA National Conference**
   Date: 7–9 August 2025
   Venue: Indaba Hotel and Conference Centre, Fourways, Johannesburg, Gauteng

The PSSA YPG is also continuously committed to voicing their professional opinion on matters that affect pharmacists in South Africa and globally. This includes the creation of 1650 jobs for public health care workers that was announced in April 2025 by the Minister of Health. Of these 1650 job opportunities, only 200 were allocated to "other healthcare professionals" which includes pharmacists. With the current shortage of pharmacists and a struggling healthcare system that critically needs our expertise and diverse knowledge, the PSSA YPG implores the Minister to revise the current allocation and consider providing more opportunities for young pharmacists and acknowledging the importance of pharmacists in the healthcare chain.
You can keep up with the PSSA YPG's activities via our newsletters and social media pages.

Website	Facebook	Instagram	LinkedIn
www.pssa.org.za/young-pharmacists-group	Young Pharmacists' Group of PSSA	@pssaypg	Young Pharmacists' Group of the PSSA.

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 https://doi.org/10.36303/SAPJ.3290

Introduction

A cough is a protective reflex that helps remove irritants such as secretions (e.g. mucus, fluids, pus) and particles (e.g. infectious agents, foreign particles, harmful substances) from the airways.[1-3] It is also one of the most common medical complaints for which individuals seek medical advice from both their doctors and community pharmacies.[1,4]

A cough is often associated with a wide array of respiratory conditions. However, it could also be a symptom of various other conditions.[1,5] Based on the duration of the cough, a cough can be classified as:[1,3,5,6]

- Acute – An acute cough typically lasts less than three weeks. Common causes include acute upper or lower respiratory tract infection (e.g. common cold, coronavirus disease 2019 [COVID-19]), an allergic condition, exposure to smoke, irritants or vaping.[1,6]
- Subacute – A subacute cough is when a cough lasts between three and eight weeks. In this case, the cough lingers while other symptoms have dissipated, for example, a post-infectious cough following a respiratory illness, or pertussis (whooping cough). Exacerbations of a chronic condition (e.g. asthma, chronic obstructive pulmonary disease [COPD]) may cause an acute or subacute cough.[1,2,6,7]
- Chronic – A chronic cough is when a cough is present for more than eight weeks. Common causes include asthma, COPD, smoking, upper airway cough syndrome (previously known as post-nasal drip syndrome), COVID-19, gastro-oesophageal reflux disease (GORD) and certain medicines such as angiotensin-converting enzyme (ACE) inhibitors. Other causes may include certain pulmonary infections (e.g. tuberculosis), lung cancer (amongst others).[1,2,6,7]

Although substantial overlap exists, this classification helps healthcare workers in identifying the most likely cause of the cough. Additional information that may be helpful includes information on whether it is a productive (wet) or non-productive (dry) cough, as well as the patient's smoking, occupational and medication history. Identifying the cause of the cough ultimately ensures that the most suitable treatment is selected for the patient.[3,5-7]

Acute coughs are mostly caused by viral infections such as the common cold or an allergic condition and are usually self-limiting and do not require treatment.[2,6] While scientific evidence for the effectiveness of cough mixtures for acute cough is debatable, many patients still find cough mixtures helpful.[2,7,8]

People presenting with a persistent cough (e.g. cough lasts for more than three weeks) or recurrent episodes of a cough should be referred to the doctor. [6,7] In addition, referral is required for those who present with "red flag" signs and symptoms such as:[1,2,6,7]

- Coughing up blood or blood in phlegm
- Shortness of breath (at rest or after exercise)
- Chest pain
- Difficulty or painful breathing
- Stridor (high-pitched noise) or other respiratory noises
- Systemic symptoms (e.g. fever, sweats, unexplained weight loss)
- Distress cough, worsening of cough or if the person cannot stop coughing
- Heartburn

Focus on Broncol Cough Linctus®

Broncol Cough Linctus® is indicated for the relief of productive or non-productive bronchial cough in colds, bronchitis and other respiratory tract disorders.[9,10] It contains dextromethorphan, ammonium chloride and dexpanthenol.

Dextromethorphan is a cough suppressant, that acts in the part of the brain that causes coughing.[1,2,7,9,10]

Ammonium chloride is used as an expectorant in productive coughs. It helps to liquefy mucosal secretions and makes it easier to expel the mucus or phlegm from the respiratory tract.[1,2,7,9,10]

Dexpanthenol has mild anti-inflammatory properties.[9,10]

Dosage and administration

Dosing recommendations:[9,10]

- Adults: 10 ml two to four times daily
- Children (6 to 12 years of age): 5 mL two to four times daily
- Children under 6 years of age: Contraindicated

Broncol Cough Linctus® should preferably be taken with meals, and may be taken undiluted or diluted in water, fruit juices, milk or tea.[9] Diabetic patients should be reminded that Broncol Cough Linctus® contains sucrose.[9]

Safety considerations

Contraindications, precautions, special warnings and side-effects

Broncol Cough Linctus® is contraindicated:[9,10]

- In people with:
  - A known hypersensitivity to any of the ingredients or excipients in the product
  - Hepatic (liver) or renal (kidney) impairment
  - An obstruction in their gastrointestinal tract
  - Bleeding disorders in which the blood does not clot properly (haemophilia)
  - Asthma, those suffering from an acute asthma attack and those who are at risks of developing respiratory failure
- In people taking:
  - Monoamine oxidase inhibitors (MAOIs) – type of antidepressant, or having taken them within the past two weeks (risk of severe and potentially life-threatening drug-drug interaction)
  - Selective serotonin reuptake inhibitors (SSRIs) – another class of antidepressants

Caution is recommended for people:

- With a history of bronchitis, emphysema, or other conditions causing persistent or chronic cough.[9,10]
- With a history of drug abuse or use of psychoactive substances. Dextromethorphan carries a potential for abuse and dependence.[8-10]
- Who are smokers. Dextromethorphan decreases coughing which could make it more difficult to get rid of mucus in the airways, which may then accumulate in the lungs and airways and predispose to possible infection.[9,10]

Dextromethorphan may cause dizziness and drowsiness and may impair the patient's ability to use machines and to drive.[9,10]

Interactions

Due to the potential risk of drug-drug interactions, it may be prudent for people who are currently using other medications to first speak to the pharmacist before they use Broncol Cough Linctus®.[9,10]

Safety considerations listed in this article are not all-inclusive. Please refer to the package insert for additional information regarding side-effects, special precautions, contraindications, potential interactions and monitoring instructions.

Prescribing information

- Cough mixtures are mainly used to provide symptomatic relief.[2]
- Expectorants may be useful for productive coughs as they make mucus less sticky and easier to cough up.[1]
- Cough suppressants given at night for a few evenings, may be helpful for a non-productive cough that disturbs sleep, if there is no serious underlying cause.[1,2,7,8] However, suppressing a productive (wet) cough may lead to mucus buildup in the lungs which may potentially increase the risk of, or worsening of, a respiratory infection.[2,8]
- Referral to the doctor or pharmacist is recommended for people presenting with a persistent cough, any red flag symptoms, as well as those who are currently taking other medications that could interact with Broncol Cough Linctus®.[7,9,10]

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COUGH CONTROL FOR UP TO *8-HOURS*[1]

✓ Opioid free cough formulation[1]

Recommend the medicine cabinet staple for wet & dry coughs, Broncol Cough Linctus[1]

S2 Reg. No. G 0931 (Act 101/1965) Broncol Cough Linctus. Each 10 mL contains: Dextromethorphan hydrobromide 30 mg, ammonium chloride 180 mg, panthenol 100 mg.
For full prescribing information refer to the Professional Information approved by the medicines regulatory authority.
Reference 1: Professional Information: Broncol Cough Linctus (Syrup).
CIPLA MEDPRO (PTY) LTD. Co. Reg. No. 1995/004182/07. Building 9, Parc du Cap, Mispel Street, Bellville, 7530, RSA. Website: www.cipla.co.za Customer Care: 080 222 6662. [1641060887]

The role of pharmacists in optimising patient outcomes to reduce the burden of tonsillitis

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Abstract

Tonsillitis is a common upper respiratory tract infection frequently encountered in pharmacy practice, with significant implications for antimicrobial stewardship. It typically involves inflammation of the palatine tonsils, most often caused by viral infections, but occasionally by bacterial pathogens such as *Streptococcus pyogenes* (Group A Streptococcus, GAS). This article reviews the anatomy, epidemiology, aetiology, complications, and management of tonsillitis, with an emphasis on evidence-based pharmacological and supportive care. It also highlights the essential role pharmacists play in optimising treatment, counselling patients and promoting rational antibiotic use to reduce antimicrobial resistance.

Keywords: tonsillitis, treatment, pharmacist, antimicrobial resistance, antimicrobial stewardship

https://doi.org/10.36303/SAPJ.3195

Introduction

The palatine tonsils, located in the lateral oropharynx between the palatoglossal and palatopharyngeal arches, are part of Waldeyer's ring – a group of lymphoid tissues that also includes the adenoids, tubal tonsils and lingual tonsils.[1] As components of the mucosa-associated lymphoid tissue (MALT), the tonsils play a key role in innate immune surveillance, facilitating antigen recognition and immune activation.[2] They are rich in T and B lymphocytes and macrophages, enabling them to mount rapid immunological responses to pathogens entering through the upper respiratory tract.[2]

Tonsillitis, the inflammation of the tonsils, remains one of the most common ENT conditions globally. It is associated with a substantial healthcare burden due to its frequency, especially in children aged 4–8 years and young adults aged 15–25 years.[3] Epidemiological studies report millions of annual cases worldwide, though current data specific to South Africa is limited. In 2019, 40 million annual cases were reported in the USA, nine million in France, and four million in Spain.[3] In the USA, 5.7% of hospital visits are attributed to a sore throat and tonsillitis. A 2023 study[4] reported 600 million symptomatic cases of tonsillitis worldwide annually. The condition impacts health systems through frequent consultations, medication use, absenteeism, and in some cases, surgical intervention.[5]

Aetiology

Tonsillitis most commonly results from viral infections, accounting for approximately 50–80% of cases. Typical viral causes include rhinovirus, adenovirus, coronavirus, influenza virus and respiratory syncytial virus—pathogens frequently associated with the common cold.[6] These cases are generally self-limiting and resolve without the need for antimicrobial therapy. Less frequent viral causes include Epstein–Barr virus (the agent of infectious mononucleosis), cytomegalovirus, HIV and rubella.[5]

The predominant bacterial cause of tonsillitis is *Streptococcus pyogenes*, a Group A Streptococcus (GAS), which is responsible for a significant proportion of cases, particularly among school-aged children and adolescents. *S. pyogenes* is of clinical importance due to its association with complications such as acute rheumatic fever and post-streptococcal glomerulonephritis.[6] Other less common bacterial pathogens include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*. In specific contexts, organisms such as *Corynebacterium diphtheriae, Treponema pallidum, Neisseria gonorrhoeae* and *Chlamydia trachomatis* should be considered, particularly in unvaccinated individuals or in those with orogenital exposure. Chronic or recurrent tonsillitis may also be associated with *Mycobacterium tuberculosis*, especially in high-burden settings such as South Africa.[6]

Transmission of infectious agents occurs primarily via respiratory droplets, direct person-to-person contact or fomites.[7] In some rare cases, animals may act as reservoirs of infection. Environmental and socio-demographic factors such as crowding, poor ventilation, seasonal variation (typically peaking in late winter and early spring) and suboptimal hygiene increase the risk of transmission.[8,9]

Notably, the incidence of tonsillitis declined during the COVID-19 pandemic, likely due to widespread public health interventions such as mask-wearing, social distancing, and enhanced hand hygiene practices, which limited the spread of respiratory pathogens more broadly.[10]

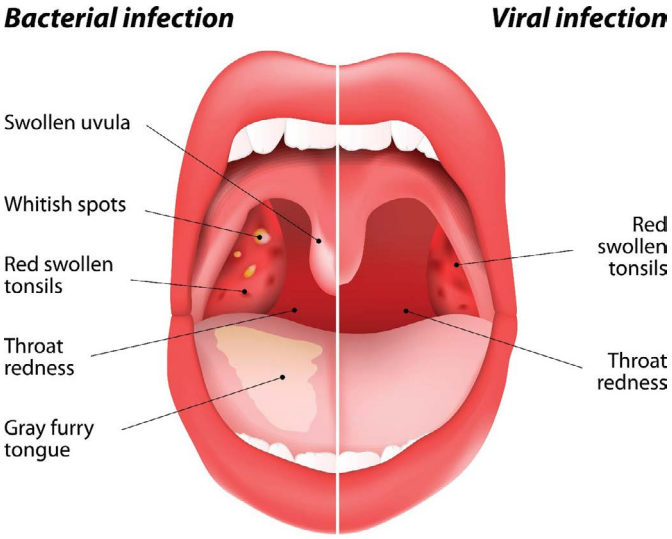

Figure 1: Vector illustration of open mouth view of tonsil inflammation caused by viral or bacterial infection (source: iStock 517419127)

Clinical presentation and diagnosis

Tonsillitis typically presents with an acute onset of sore throat, odynophagia (painful swallowing) and fever. On clinical examination, the tonsils appear erythematous and swollen, often with white or yellow exudates (Figure 1).[11] Associated features may include halitosis, headache, malaise, cervical lymphadenopathy and occasionally referred otalgia. In some patients, particularly young children, symptoms may also include nausea, vomiting, abdominal pain and irritability.[11]

Viral tonsillitis often co-presents with symptoms of an upper respiratory tract infection, such as nasal congestion, rhinorrhoea, cough, hoarseness and conjunctivitis. These features suggest a viral rather than bacterial origin.[11] In contrast, bacterial tonsillitis, particularly due to *S. pyogenes*, typically has a more abrupt onset, higher fever, absence of cough and more prominent tonsillar exudates and tender anterior cervical lymph nodes.[11-12]

In children, tonsillitis may manifest with a barking cough, hoarseness and respiratory distress, especially if the adenoids are concurrently inflamed. Very young children may present non-specifically with symptoms such as refusal to feed, excessive drooling or lethargy.[9,13]

Accurately distinguishing between viral and bacterial aetiologies is essential to avoid inappropriate antibiotic use and to minimise the risk of antimicrobial resistance.[14] Clinical scoring systems such as the Centor or McIsaac criteria may aid decision-making by assessing features including fever, tonsillar exudate, absence of cough and lymphadenopathy. A higher score suggests a greater likelihood of streptococcal infection.[6-7]

Rapid antigen detection tests offer quick identification of *S. pyogenes*, but their sensitivity can be limited, especially in children.[7,14] A throat culture remains the gold standard for diagnosis, with high sensitivity and specificity, although it requires 24–48 hours for results.[6,15] Serological testing may be useful in select cases, particularly when viral causes such as Epstein–Barr virus are suspected.[16]

Ultimately, diagnosis should integrate the clinical history, physical examination, and where available, laboratory testing, to guide appropriate management and reduce unnecessary antibiotic use.

Complications

Non-suppurative complications of *S. pyogenes* tonsillitis includes acute rheumatic fever, post-streptococcal glomerulonephritis and scarlet fever.[17-18] Acute rheumatic fever typically presents two to four weeks after the initial infection and is a systemic inflammatory disease that may affect the heart (often as pancarditis), joints, central nervous system (notably as Sydenham chorea) and skin.[18] Importantly, acute rheumatic fever is preventable with timely and appropriate antibiotic treatment of the initial streptococcal infection.[18] In contrast, post-streptococcal glomerulonephritis arises one to three weeks post-infection due to immune complex deposition in the glomeruli, leading to haematuria, hypertension and renal dysfunction.[19] Unlike rheumatic fever, post-streptococcal glomerulonephritis is not preventable by antibiotics, underscoring its distinct pathophysiology.[19] Scarlet fever, another immune-mediated complication, results from infection with toxin-producing GAS strains. It is characterised by a fine sandpaper-like rash, strawberry tongue, and fever, and though dramatic in appearance, it typically resolves with appropriate antibiotic therapy.[20]

Role of pharmacists

Acute tonsillitis can significantly affect a patient's quality of life through symptoms such as sore throat, fever and difficulty swallowing. While most cases are viral and self-limiting, bacterial tonsillitis—especially when caused by *S. pyogenes*—requires timely and appropriate antibiotic therapy to prevent complications.[2] However, the widespread misuse and over prescription of antibiotics in treating tonsillitis has contributed to the growing global concern of antimicrobial resistance.[21] Pharmacists, as accessible healthcare professionals, play a central role in guiding evidence-based treatment, supporting antimicrobial stewardship and educating patients on the appropriate use of medications.[22]

Medical management

Supportive care remains the foundation of acute tonsillitis treatment, especially in viral cases, with key goals including symptomatic relief (fever reduction, inflammation control and pain alleviation) along with maintenance of adequate hydration and nutrition.[8] If symptoms escalate or complications arise—such as airway obstruction or severe dehydration—patients may require additional interventions including intravenous fluids, systemic corticosteroids or humidified oxygen.[8]

In viral tonsillitis, antibiotics are not indicated. Management involves rest, hydration and symptomatic relief. Most cases resolve within 7–10 days. Sore throat persisting beyond two weeks, or

recurrent episodes, warrant evaluation for chronic tonsillitis, which may require surgical intervention.[23,24-25]

For bacterial tonsillitis, particularly cases caused by *S. pyogenes*, antibiotic therapy is warranted to reduce symptom duration, prevent complications such as acute rheumatic fever and limit transmission.[7] First-line therapy is phenoxymethylpenicillin (penicillin V) due to its narrow spectrum, low cost and proven efficacy.[9] The dose depends on the patient's age and weight (Table I).[4,7,9] Penicillin V is best taken on an empty stomach to enhance absorption. A 10-day course is standard to prevent serious sequelae like rheumatic fever. Amoxicillin is an acceptable alternative.[9]

For patients with non-anaphylactic penicillin allergies, cephalosporins (e.g. cefadroxil, cephalexin) may be used. For those with Type 1 hypersensitivity reactions, however, macrolides (e.g. erythromycin, clarithromycin, azithromycin) or clindamycin are recommended.[4] Azithromycin and clarithromycin, due to their significantly longer half-lives, may be prescribed for shorter durations (3–5 days), although resistance rates are increasing globally.[2,7]

In patients unlikely to complete a full oral course, a single intramuscular injection of benzathine penicillin G is effective.[4]

Table I: Penicillin's for acute tonsillitis

Phenoxymethylpenicillin (Penicillin V) oral
Adults and adolescents: 500–1 000 mg orally, 2–3 times daily for 10 days.
Children 1–12 years: 250 mg orally 2–3 times daily.
Children > 12 years: 500 mg orally 2–3 times daily.
Weight-based dosing: 15–50 mg/kg/day in 2–3 divided doses, not exceeding the adult dose.
Amoxicillin oral
Adults: 500 mg three times daily for 10 days.
Children under 40 kg: 50 mg/kg/day divided in 2–3 doses (max 1500 mg/day).
Benzathine IM penicillin single dose
≥ 27 kg: 1.2 million units IM once.
< 27 kg: 600,000 units IM once.

Antibiotics not recommended for tonsillitis include sulphonamides, tetracyclines and fluoroquinolones, due to resistance or limited efficacy against *S. pyogenes*.[9]

Corticosteroids (e.g. dexamethasone or prednisone) may be used in cases with severe inflammation, particularly when swallowing or breathing is compromised.[23]

Over-the-counter (OTC) analgesics such as paracetamol, ibuprofen or naproxen are widely used to relieve pain and fever. While effective, NSAIDs should be used cautiously due to risks of gastric irritation and ulceration with prolonged use.[26] In children, ibuprofen suspension and combination formulations with pseudoephedrine or nimesulide (where approved) may be used, although the latter is not universally recommended.[23]

Topical therapies (e.g. throat sprays, oral rinses, lozenges) can offer local symptom relief. Many contain local anaesthetics, anti-inflammatory agents or antiseptics.[23] Lozenges should be avoided in children under four due to choking risk.[27] Oral rinses are generally suitable for children aged 12 and above who can reliably gargle without swallowing. Throat sprays are safe from age six and up.[27]

In addition to conventional medical treatments, several complementary and alternative medicine (CAM) approaches have been explored for managing tonsillitis, particularly in cases of viral origin where antibiotics are not indicated. Common supportive measures include saltwater gargles, warm fluids and herbal teas containing soothing agents like honey, pectin and glycerine.[27] Among herbal preparations, BNO 1030 (Imupret®), a phytotherapeutic blend of Althea root, chamomile flowers, horsetail herb, walnut leaves, yarrow herb, oak bark and dandelion herb, has demonstrated efficacy in reducing symptoms of acute non-bacterial tonsillitis in children when used alongside standard symptomatic therapy.[28] Clinical studies have reported significant symptom relief and reduced need for antipyretics without notable adverse effects.[28] Similarly, EPs 7630 (Umckaloabo®), an extract from *Pelargonium sidoides* roots, has shown effectiveness in alleviating symptoms of acute tonsillopharyngitis in children. A double-blind, placebo-controlled trial found that EPs 7630 significantly reduced tonsillitis severity scores compared to placebo, with good tolerability.[29]

Carvacrol, a compound found in oregano and thyme essential oils, exhibits anti-inflammatory and antibacterial properties. *In vitro* studies have demonstrated its ability to suppress inflammatory markers in human tonsil epithelial cells and exert bactericidal effects against *GAS*, suggesting potential as a supportive therapy in streptococcal pharyngitis.[30]

Traditional remedies such as Kanchnara Guggulu and Tankana-Madhu Pratisarana have been evaluated in Ayurvedic medicine for managing tonsillitis (Tundikeri) in children. A clinical study reported that these treatments led to significant improvements in symptoms, indicating their potential as safe and effective options in paediatric populations.[31]

While these CAM therapies show promise, they should complement, not replace, evidence-based medical treatments. Patients are advised to consult healthcare professionals before initiating any alternative therapies to ensure safety and appropriateness within their overall treatment plan.

Antimicrobial resistance (AMR)

Antibiotic consumption and antimicrobial resistance (AMR) are closely linked. When antibiotics are used inappropriately, whether through unnecessary prescribing, incorrect dosing or insufficient treatment duration, they exert selective pressure that favours the survival and proliferation of resistant bacterial strains.[32] This is particularly problematic in the treatment of self-limiting conditions such as acute viral tonsillitis, where antibiotics are often prescribed despite minimal or no clinical benefit.[11,32]

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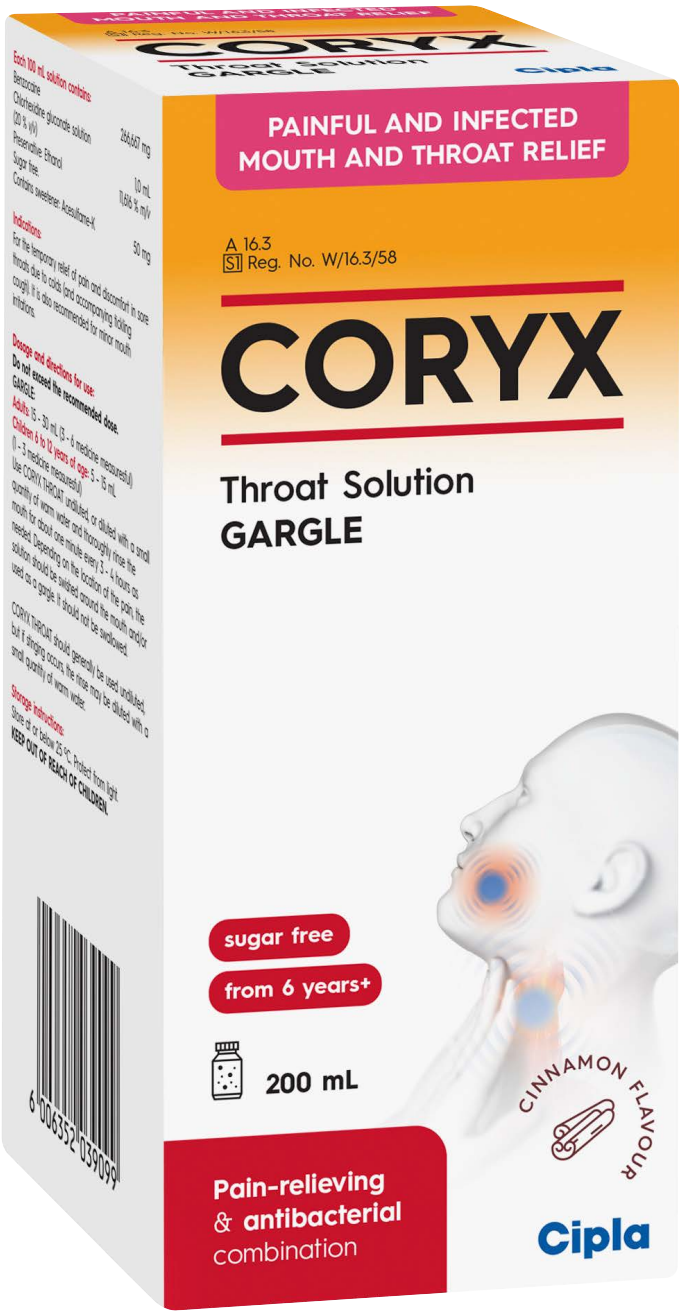

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200 mL

S1 W/16.3/58. Coryx Throat (Solution). Each 100 mL of solution contains: benzocaine 266,667 mg, chlorhexidine gluconate solution (20 % *v/v*) 1,0 mL. For full prescribing information, refer to the Professional Information approved by the medicines regulatory authority.

References: 1. Professional Information: Coryx Throat (Solution). CIPLA MEDPRO (PTY) LTD. Co. Reg. No. 1995/004182/07. Building 9, Parc du Cap, Mispel Street, Bellville, 7530, RSA. Website: www.cipla.co.za Customer Care: 080 222 6662. [1630358304]

Multiple studies have demonstrated a high prevalence of antibiotic-resistant organisms in patients with recurrent tonsillitis.[33] A study by Jyothsna et al. reported significant resistance among isolates of *Streptococcus* species and other pathogens, with the highest resistance observed against ampicillin, followed by cefazolin and ceftriaxone.[34] Additional data have revealed concerning resistance rates to amoxicillin, azithromycin and clindamycin, all of which are frequently prescribed in the management of acute bacterial tonsillitis.[33]

The increasing resistance observed in *S. pyogenes* and *S. aureus* is of particular concern. While *S. pyogenes* remains largely susceptible to penicillin, treatment failures have been reported.[35] These failures may not be due to intrinsic resistance, since *S. pyogenes* does not produce beta-lactamase, but rather due to beta-lactamase–producing co-pathogens in the oropharynx such as *S. aureus* and *H. influenzae*, which may inactivate penicillin before it reaches the target organism.[35] Other factors contributing to therapeutic failure include incorrect antibiotic selection, suboptimal dosing, inadequate treatment duration and poor patient adherence.[36]

Macrolides (e.g. azithromycin, erythromycin), often used as alternatives in penicillin-allergic patients, are also facing rising resistance rates, particularly in regions such as North America and Europe, where empirical use is common. This trend limits their utility and reinforces the need for judicious prescribing.[36]

While data on resistance related to OTC topical antibiotics for sore throat is limited, *in vitro* studies raise concerns.[37] Westgate et al. reported reduced susceptibility of *S. pyogenes* and *S. aureus* to commonly used OTC topical agents such as tyrothricin, gramicidin, bacitracin and neomycin. Though topical agents may offer symptomatic relief, their widespread, unregulated use may contribute to local resistance development.[32]

These findings reinforce the need for targeted antibiotic therapy based on accurate diagnosis and for improved antimicrobial stewardship to curb resistance emergence in community and clinical settings.

Role of pharmacists in antimicrobial stewardship (AMS)

Prescription patterns for antibiotics vary both internationally and regionally. Numerous factors, including cost, physician choice, antibiotic susceptibility and pathogenic organisms, contribute to this difference.[38] Antimicrobial stewardship is a corrective action which aids in improving prescription practices, monitors and controls broad spectrum antibiotic use, improves clinical outcomes in patients and reduces emergence of antibiotic-resistant pathogens.[39]

Overprescription had led to irrational antibiotic use for tonsillitis, resulting in bacterial resistance and treatment failure. In the clinical capacity, the problem stems from prescribing behaviours, whereby national guidelines are not being adhered to. Additionally, improperly performed clinical assessments lead to inaccurate aetiology, and hence treatment is misinformed.[40] Antimicrobial therapy for acute tonsillitis should be targeted, with a correct antibiotic, dosage and a duration that will likely eliminate the pathogen.[36]

Walijee et al.[11] recommends a delayed antibiotic prescription strategy. In this practice, patients are advised against taking any antimicrobial immediately after onset and prescription is delayed for at least seven days. Patients are also recommended to seek medical advice to manage the condition. While penicillin administered for 10 days remains the most common treatment, alternative antibiotics such as cephalosporins and certain macrolides have also proven to be clinically effective for a shorter period: 5–7 days.[36] At the same time, over-reliance on macrolides as an alternative therapy should be discouraged, and instead these antibiotics should only be prescribed in cases of patients with type 1 penicillin allergy.[36] Rational prescribing of antibiotics should be adopted. Antimicrobial resistance, poor patient compliance and additive problems such as treatment costs and adverse effects can be combated by reducing the number of prescribed antibiotics.[38]

Community pharmacists are the first point of contact for the general populace, especially when patients are seeking medical advice regarding treatment of upper respiratory tract infections such as tonsillitis.[41-42] In recent years, the role of a pharmacist has changed from solely being dispensers or distributors of medicines to an important role-player in healthcare management.[43] Their accessibility and expertise to medicines allow them to help diagnose patients, educate them on treatment options and manage common conditions.[42]

Hence, it is imperative that pharmacists are well-versed in disease management and can minimise complications. In a study by Aldomah et al.,[41] the majority of pharmacists cited azithromycin as the first line of therapy for tonsillitis, despite the treatment guidelines recommending penicillin as the mainstay antibiotic. Additionally, most pharmacists were unaware of the use of corticosteroids as an adjuvant therapy. Mansour and Al-Kayali's[43] 2017 study demonstrated inadequate knowledge of pharmacists regarding antibiotic resistance, as many chose to dispense broad-spectrum antibiotics for tonsillitis, oblivious to the threat of the emergence of resistance.

While antibiotics are largely prescription-based medicines, they can still be obtained without prescription from drug outlets or pharmacies in several countries.[43] The problem of OTC antimicrobials is especially rampant in South America, Africa and Asia, where drug regulations governing sales and distribution of medicines are either inadequate or not enforced. This problem has also plagued some developed countries.[44] In pharmacies, especially in low and middle-income countries, patients often rely on the pharmacist consultation and advice due to economic constraints.[43] Additionally, many consumers seek OTC products and antibiotics for sore throat or upper respiratory tract infections with similar symptomatic profiles, unaware if the condition is caused by a virus or a bacterium.[42]

Education and training are cornerstones of AMS. Pharmacists are important in educating not only patients, but also healthcare

professionals engaged in poor prescribing practices and members of the public.[39] They play a significant role in disease management, discouraging self-diagnosis, clearing common misconceptions and dispelling myths surrounding treatment of self-limiting conditions such as tonsillitis. They ought to advocate for the prudent, safe and suitable use of medicine.[42] Being a key player in healthcare management, they have a responsibility to be a reliable source of information for patients, especially in terms of disease intervention, treatment plans and optimised use of antibiotics.[39]

In terms of acute respiratory infections, pharmacist intervention also includes informing patients about risks and benefits of antibiotic usage, considering diagnosis and clinical management. This is a shared decision-making approach, likely to improve patient health outcomes, while providing satisfaction.[45]

In developed countries, especially the USA, UK and France, clinical pharmacists are actively involved in AMS programmes, whereby they receive training to equip them in lowering antibiotic consumption in patients. They oversee good prescribing practices, manage antimicrobial drugs, and review relevant policies, audits and feedback that play a role in monitoring antibiotic consumption.[46] Prescription surveillance systems, coupled with restrictive or enablement interventions have been shown to improve adherence to antimicrobial policies.[39] However, it should be noted that although such systems are readily available in hospitals, they might not be accessible in communities.[39]

Evidence synthesis by Wu et al.[45] showed that pharmacist's involvement in public health education programmes reduced inappropriate antibiotic prescriptions by 20% in primary healthcare settings for acute respiratory infections. The study also suggested how shared decision-making, usage of viral prescriptions (non-antibiotic) could be implemented in patient counselling, especially in the management of conditions such as tonsillitis, otitis media and sinusitis.

The above evidence underscores the significance of antibiotic stewardship, targeted therapy and enhanced diagnostic techniques to diminish wasteful antibiotic prescriptions and alleviate resistance development in recurring illnesses.[33]

Conclusion

Tonsillitis is generally a self-limiting condition, and while medical management may offer symptomatic relief, a definitive diagnosis is essential before initiating antibiotic therapy, particularly given the alarming rise in antimicrobial resistance. There is a pressing need to improve prescribing practices for conditions like tonsillitis and to strengthen AMS efforts. Pharmacists, often serving as the first point of contact for patients, play an important role in AMS by raising awareness, educating both patients and the public, and promoting responsible prescribing and dispensing practices.

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Depression unveiled: a comprehensive review of pathophysiology and treatment advances

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Abstract

Depression is one of the most commonly diagnosed mental health disorders among adults and is currently the third leading cause of disease worldwide. Depression, also referred to as major depressive disorder (MDD), poses a significant global health challenge, affecting over 300 million individuals worldwide. In sub-Saharan Africa, neuropsychiatric conditions account for nearly 10% of the disease burden, with depression being the most frequently diagnosed disorder. Clinically, depression manifests through symptoms such as feelings of worthlessness, cognitive and sleep disturbances, and suicidal ideation, with major depression representing the predominant subtype. Its complex pathogenesis has been extensively investigated, incorporating hypotheses related to genetic predisposition, neurotransmitter dysregulation, and hypothalamic-pituitary-adrenal (HPA) dysfunction, among others. While both pharmacological and non-pharmacological interventions demonstrate efficacy, antidepressant medications remain the cornerstone of treatment. Untreated depression can lead to widespread emotional, behavioural, and physical health complications, significantly impairing quality of life. This review reports current hypotheses regarding the underlying pathophysiology of depression and evaluates therapeutic strategies with an emphasis on the pharmacological profile of the classes used to treat depression.

Keywords: depression, anti-anxiety, anti-depressants, major depressive disorder, selective serotonin re-uptake inhibitors

https://doi.org/10.36303/SAPJ.3284

Introduction

Major depressive disorder (MDD) is the most widespread mental health disorder worldwide.[1] It is marked by persistent depressed mood, loss of interest or pleasure in previously enjoyable activities, recurrent thoughts of death, and various physical and cognitive symptoms.[2]

It is a major contributor to the global disease-related burden among adolescents and young adults.[3] Worldwide, there has been a 59% increase in the cases of MDD observed from 172.27 million in 1990 to 274.80 million in 2019.[4] This highlights the growing burden of the disease and the need for effectual interventions.[5] The prevalence is greater in females compared to males. Adolescence and early adulthood is a developmental stage characterised by hastened biological, psychological and social changes which amplifies the vulnerability to various mental health disorders, includding MDD.[4] There are significant long-term consequences that are associated with the early onset of depression during the developmental stages. When depression remains untreated or inadequately managed, it increases the risk of chronic health problems, substance abuse, and impact on psychosocial and economic functioning.[4,5] The impact of depression is profound, significantly impairing quality of life and daily functioning.[6] It can interfere with work, education, and personal relationships. Globally, depression and anxiety account for an estimated 12 billion productive working days each year, costing the economy $333.7 billion ($382.4 billion in 2023 US dollars) annually.[7,8]

Depression is a complex condition influenced by a range of factors. Genetic predispositions, such as heritability and gene-environmental interactions, play a role.[9] Environmental influences, including early life trauma, major life stressors, and chronic illness, are also important contributors.[9,10] Psychosocial elements like poor social support, loneliness, and caregiver burden further increase the risk, as do neuroendocrine and neurochemical imbalances associated with certain brain and hormonal disorders.

Standard therapeutic approaches to the management of depression include pharmacotherapy, particularly antidepressants, and psychological therapies such as cognitive-behavioural therapy (CBT).[11] Although there are effective treatments available, depression often goes unrecognised and is insufficiently treated.[12] Historically, this has been linked to stigma and challenges in symptom detection.

Pathophysiology

The pathophysiology of depression is not fully explainable, but significant progress has been made in identifying key neurobiological systems and mechanisms (as per Figure 1), implicated in its development. The pathophysiological findings of depression include dysregulation in neurotransmitter systems, neuroendocrine and inflammatory pathways, structural and functional brain alterations, genetic and epigenetic influences, and disruptions in neuroplasticity.[13]

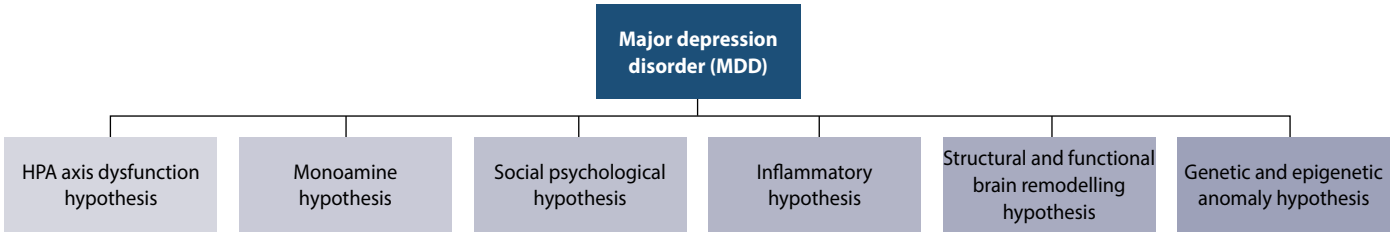

Figure 1: An outline of the hypotheses of MDD pathogenesis[40]

1. Neurotransmitter dysregulation

The **monoamine hypothesis** remains a foundational theory in the pathophysiology of depression, suggesting that deficits in central monoamines, primarily serotonin (5-HT), norepinephrine (NE), and dopamine (DA) play a critical role in symptom manifestation.[13] Reduced synaptic availability of these neurotransmitters in key brain regions such as the prefrontal cortex, hippocampus, and amygdala correlates with core symptoms of depression, including anhedonia, low mood, and cognitive disturbances. Pharmacological evidence supports this hypothesis, as most antidepressants act by increasing the synaptic concentrations of monoamines via inhibition of reuptake or enzymatic degradation.[14] Serotonin (5-HT) is widely distributed throughout the nervous system and its deficiency can lead to depression, phobias, anxiety, and other mental health disorders in patients. In the brain, dopamine (DA) is a dominant transmitter that regulates behaviour and is a precursor to epinephrine and norepinephrine (NE).[14]

There is evidence that depression is caused by an **imbalance in the GABA and glutamate** systems.[15] Glutamate is the primary excitatory neurotransmitter and contributes to synaptic plasticity, cognitive activities, and motivational and emotional behaviour in the brain. Researchers have found elevated levels of glutamate in the blood, brain and cerebrospinal fluid (CSF), of patients with depression as well as N-methyl-D-aspartate receptor (NMDAR) subunit disturbances. The inhibition of NMDAR function by ketamine for example, has antidepressant effects and protects the hippocampal neurons from stress-induced morphological changes.[15] Numerous studies have demonstrated that MDD patients have defects in GABA neurotransmission function. Brain GABA levels in MDD patients were lower than those in healthy controls in the prefrontal cortex.

2. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation

Hyperactivity of the HPA axis is one of the most consistently observed biological abnormalities in patients with depression. Chronic stress activates this system, resulting in excessive secretion of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and ultimately cortisol.[13] The glucocorticoids interact with their receptors in multiple target tissues within the HPA axis, where they act as feedback inhibitors of both ACTH production in the pituitary corticotropes and CRH production in the hypothalamus. Disturbances of the HPA axis induced by stress have been shown to be associated with depression because of increased production of cortisol and insufficient inhibition of glucocorticoid receptor regulatory feedback.[16]

3. Inflammatory and immune system activation

Emerging evidence supports the role of immune dysregulation in depression because most patients have been seen to have increased levels of inflammatory molecules.[17] The roots of the immune hypothesis of depression can be traced back to the early 1990s, otherwise known as the 'cytokine hypothesis of depression'.[18] Increased levels of pro-inflammatory cytokines—such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)—have been observed in depressed individuals. These cytokines can alter neurotransmitter metabolism, reduce the availability of tryptophan (a serotonin precursor), and impair synaptic plasticity.[17]

4. Neuroplasticity and neurogenesis deficits

Neuroplasticity is the brain's ability to adapt structurally and functionally in response to environmental and internal stimuli. A significant body of evidence suggests that depression causes changes in neuroplasticity in specific regions of the brain which are correlated with symptom severity, negative emotional rumination as well as fear learning.[19]

Neuroimaging studies have identified structural abnormalities in several brain regions involved in emotion regulation and cognitive processing. Reductions in grey matter volume have been reported in the hippocampus, anterior cingulate cortex, and dorsolateral prefrontal cortex.[20] Functional alterations in neural circuits—such as hyperactivity in the amygdala and hypoactivity in the prefrontal cortex—are also common, correlating with heightened emotional reactivity and impaired executive function, respectively.

Depression is correlated with atrophy of neurons in the cortical and limbic brain regions that control mood and emotion. High levels of plasmatic cortisol have been observed to suppress neuroplasticity in the hippocampus. Decreased expression of brain-derived neurotrophic factor (BDNF), particularly in the hippocampus and prefrontal cortex, is associated with reduced synaptic connectivity, impaired learning, and mood regulation. Antidepressant pharmacotherapy has been shown to upregulate BDNF which activates the tyrosine kinase receptors and triggers an intracellular cascade involving cAMP-dependent protein kinase A, mitogen-activated protein kinase as well as other signalling molecules.[21]

5. Genetic and epigenetic influences

Major depressive disorder is likely to have a heritability rate of approximately 31–42%.[22] Several depression risk loci have been identified. This evidence shows that depression is influenced by genetic factors.[23,24] Gene-environment interactions, particularly involving early-life stressors, play a crucial role in modulating vulnerability through epigenetic mechanisms such as DNA methylation and histone modification.[20]

Clinical manifestation

Depression presents a combination of psychological and somatic symptoms. Core features include persistent depressed or irritable mood and/or lack of interest or pleasure in activities.[25] Patients often report feelings of guilt, worthlessness or hopelessness, and reduced energy or fatigue. Cognitive symptoms such as diminished ability to think or concentrate and indecisiveness are common.[25] Somatic features include changes in appetite or weight, insomnia or hypersomnia, and psychomotor agitation. Many patients also have recurrent thoughts of suicidal ideation. In children and adolescents, mood may present more as irritability than classic sadness.

Depression also presents with substantial functional impairment. A South African survey showed that over 90% of respondents with depression reported significant disruption in work, social, or home activities.[26] The burden of depression is seen in disability and suicide with about one in eight deaths worldwide in young adults are linked to suicide, many of which involve depression.[27] A major depressive episode must last ≥ 2 weeks by definition, but many episodes extend for months if untreated. Untreated mental health disorders escalate patient morbidity leading to functional impairment and increases the risk of suicide attempts.[28,29] Furthermore, if antidepressant pharmacotherapy is initiated later than six months since the first onset of a depression episode, the chance of the patient attaining remission significantly decreases.[30] The importance of early recognition and treatment of depression in patients is highly emphasised.[30]

Persistent depressive disorder (PDD), also known as dysthymia, involves chronic depressive symptoms lasting two years or more.[31] The severity of symptoms is lower than in acute MDD but often includes low energy, low self-esteem, hypersomnia or insomnia, appetite changes, and difficulty concentrating. By definition an individual living with PDD has not gone more than two months symptom-free.[31] Due to its chronic nature, PDD tends to cause cumulative impairment and it "is often more disabling than episodic major depression".[32]

Other notable subtypes include seasonal affective disorder (SAD), a pattern of MDD episodes that recur seasonally. This typically manifests as depressive episodes in late autumn/winter that remit by spring.[33] Prevalence of SAD varies by latitude and study methods but is generally estimated around 1–10%.[34,35]

Postpartum depression (PPD), is a form of perinatal depression which refers to MDD onset during pregnancy or the first year after childbirth.[36] Common symptoms include mood swings, mild elation, irritability, tearfulness, fatigue, and confusion.[37] A recent global meta-analysis found PPD in about 17% of new mothers worldwide, with the highest rates of approximately 40% reported in Southern Africa.[36]

Atypical depression is defined by a specifier of mood reactivity plus ≥ 2 "reversed" neurovegetative symptoms.[38] Diagnosis of atypical depression requires mood reactivity (ability to feel better temporarily in response to a positive life event) plus at least two of the following symptoms: significant overeating (hyperphagia), weight gain, excessive sleep, or a heavy, leaden feeling in the limbs.[38]

Bipolar disorder, previously known as manic depressive illness, is a severe chronic mood disorder characterised by episodes of mania, hypomania, and alternating or intertwining episodes of depression.[39] In a worldwide mental health survey, the prevalence of bipolar disorders was consistent across diverse cultures and ethnic groups, with an aggregate lifetime prevalence of 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, 1.4% for subthreshold bipolar disorder, and 2.4% for the bipolar disorder spectrum. Bipolar I disorder presents with at least one manic episode, although major depressive episodes are typical but they are not required for diagnosis.[39] Bipolar II disorder presents with at least one hypomanic episode and one major depressive episode.

Additionally, other less prevalent DSM-defined mood disorders include premenstrual dysphoric disorder, disruptive mood dysregulation disorder, and substance/medical-induced depressive disorder.[40]

Management

1. Non-pharmacological management

1.1 Psychotherapy

Psychotherapy is an essential part of the treatment of depression. It is considered the first treatment for mild depression, when used in combination with pharmacotherapy, improves treatment response, quality of life and reduces the risk of relapse. Effective psychotherapy techniques include CBT, inter-personal therapy (IPT)**,** and other structured psychotherapies, have strong evidence of effectiveness and can support evidence that psychotherapy can be as effective for many patients as drug therapy.[41,42] Evidence suggests that psychotherapy and antidepressant pharmacotherapy have broadly similar effects on the severity of depression, although some analyses suggest a slight superiority of the pharmacotherapy on average. Importantly, psychotherapy also offers long-term benefits such as improved resistance skills and relapse prevention.[41,42]

1.2 Electroconvulsive therapy (ECT)

Electroconvulsive therapy (ECT) is a psychological therapy that deals with the treatment of depression and other mental health

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disorders. It involves applying electrical energy to the scalp to induce seizures. ECT increases the concentration of GABA in the cortex and increases the function of serotonin, making it more effective than antidepressants pharmacotherapy, although it is usually a reserved treatment due to its higher risk of side effects.[43] The decision to use ECT varies depending on severity and patient preferences. Although ECT is more effective than antidepressant pharmacotherapy, it is usually reserved for case-resistant treatments due to the relatively high risk of side effects.[43,44]

1.3 Complementary therapies

Other approaches, such as naturopathy, can be integrated into a comprehensive treatment plan, but the evidence is inconclusive, therefore these methods should not replace standard care.[12]

2. Pharmacological management

Pharmacotherapy is the cornerstone of the treatment of moderate to severe depression. The primary aim during the acute phase of a major depression episode is to achieve symptom remission and restore the functional baseline. The mechanism of action and adverse effect profiles vary depending on the class of antidepressants.

2.1 Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are first-line pharmaceutical treatments due to their proven efficacy and safety. They work by inhibiting the reabsorption of serotonin and thus increasing the level of serotonin in the brain. SSRIs are generally well tolerated, with common side effects, including sexual dysfunction and gastrointestinal symptoms.[45-47]

2.2 Serotonin-norepinephrine reuptake inhibitors (SNRIs)

SNRIs are also used as first-line options. They exert their effect by inhibiting the reuptake of both serotonin and norepinephrine, making them effective for both depression and chronic pain conditions.[45]

2.3 Tricyclic antidepressants (TCAs)

TCAs inhibits the reabsorption of serotonin and norepinephrine, but they are also associated with action on muscarinic, histaminic and alpha-adrenergic receptors. This results in more side-effects than SSRIs. They are indicated for major depression, anxiety, sleep disorders and chronic pain. Common side effects include constipation, dry mouth, dizziness, weight gain, orthostatic hypotension and sedation.[35,48]

2.4 Monoamine oxidase inhibitors (MAOIs)

MAOI were one of the first antidepressants to be developed. They act by inhibiting the monoamine oxidase enzymes (MAO-A and MAO-B) increasing levels of neurotransmitter. Similar enzymes break down dopamine, norepinephrine, and serotonin. Due to safety and nutrition concerns MAOIs are rarely used due to dietary

Table I: Antidepressant drug classes, examples and common side-effects[45-47]

Class	Generic names	Mechanism	Indications	Side Effects
Monoamine oxidase inhibitors (MAOI)	• Moclobemide • Tranylcypromine	• Inhibits monoamine oxidase which degrades dopamine, norepinephrine and serotonin.	• Major depressive disorder • Anxiety	• Drowsiness • Fatigue • Decreased sexual function • Hypertensive crisis
Selective serotonin reuptake inhibitors (SSRIs)	• Citalopram • Escitalopram • Fluoxetine • Sertraline	• Inhibits reuptake of serotonin	• Major depressive disorder • Anxiety disorders	• Headache • Drowsiness • Suicidal ideation • Chanes in sexual behaviour
Serotonin norepinephrine reuptake inhibitors (SNRIs)	• Duloxetine • Desvenlafaxine	• Inhibits reuptake of serotonin and norepinephrine	• Major depressive disorder • Anxiety disorders • Diabetic peripheral neuropathic pain	• Dizziness • Fatigue • Orthostatic hypotension
Tricyclic antidepressants	• Amitriptyline • Imipramine • Nortriptyline	• Inhibits reuptake of serotonin and norepinephrine	• Major depressive disorder • Anxiety disorders • Sleep disorders • Chronic pain syndromes	• Dry mouth, blurred vision • Weight gain • Sedation • Sexual dysfunction
Triazolopyridine	• Trazodone	• Inhibits reuptake of serotonin and serotonin receptor antagonist	• Depression • Mixed anxiety	• Priapism
Phenylpiperazine	• Nefazodone	• Moderately inhibits serotonin and norepinephrine inhibitor	• Major depressive disorder	• Hepatotoxicity
Aminoketone	• Bupropion	• Selectively inhibits reuptake of dopamine and norepinephrine	• Depression • Smoking cessation	• Tremors • Dose-dependent seizures • Sweating
	• Mirtazapine	• Blocks presynaptic ά2-adrenergic autoreceptors, 5-HT2 and 5-HT3	• Major depressive disorder	• Sedation

restrictions therefore are reserved for treatment-resistant cases.[45,46] Table I gives a summary of the antidepressant classes, examples in each medication class, indications and common side effects.

In the event where the patient experiences treatment-resistant depression (TRD), augmentation strategies are recommended after two failed antidepressant trials.[49] The Food and Drug Administration (FDA)-approved adjunctive agents include atypical antipsychotics such as aripiprazole, quetiapine, olanzapine/fluoxetine, risperidone which all significantly increase response and remission rates when added to an antidepressant.[50] Lithium augmentation has strong evidence and is a guideline first-line augmenter for TRD since it significantly improves response and reduces suicide risk. Thyroid hormone (T3) augmentation is also evidence-based, showing higher response rates than placebo when added to antidepressants.[50] Other augmenters with evidence include stimulant-like agents such as modafinil and second-generation antipsychotics such as aripiprazole and quetiapine which are supported for TRD. Lastly, ketamine (an NMDA antagonist) produces rapid antidepressant effects in TRD.[51] Intravenous ketamine has been shown to significantly improve symptoms in TRD, often within hours, though durability is limited.[51]

New antidepressant medications have been introduced recently. Gepirone extended-release (a 5-HT1A partial agonist) received FDA approval in 2023 for MDD based on clinical trials showing moderate efficacy.[45] Lumateperone, an atypical antipsychotic with serotonin and dopamine modulation, showed significant benefit in clinical trials of mixed-feature depression and is being explored for the treatment of MDD.[52] However, these medications are not yet on the market.

Conclusion

The management of depression requires a comprehensive, patient-centred approach that integrates both non-pharmacological and pharmacological strategies. Psychotherapy, including CBT and interpersonal therapy, offer significant benefits in symptom reduction, coping skill development, and relapse prevention, particularly in mild to moderate cases. For treatment-resistant or severe depression, electroconvulsive therapy remains a valuable and highly effective option. Pharmacological interventions are essential, especially for moderate to severe or persistent depression. First-line agents such as SSRIs and SNRIs are favoured for their efficacy and tolerability, whilst TCAs and MAOIs may be considered in specific clinical contexts, despite their more complex side effect profiles. The choice of treatment should be guided by the severity of symptoms, patient preferences, previous treatment responses, and the presence of comorbidities. Ultimately, a collaborative, tailored treatment plan that may include both pharmacotherapy and psychotherapy offer the best outcomes in achieving remission and restoring quality of life for individuals living with depression.

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Focus on Allopurinol

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 https://doi.org/10.36303/SAPJ.3193

Introduction

Urate saturation of extracellular fluids results in hyperuricaemia.[1] The deposition of this monosodium urate (MSU) in joints, soft tissues and bones, triggers an inflammatory arthritis and can manifest in many forms including acute gout flare, chronic gouty arthritis and tophaceous gout (formation of tophi).[1] Factors that lead to changes in the extracellular urate concentration have the potential to trigger a gout flare-up and include stress (mainly due to medical conditions), dietary choices and drugs, including aspirin, diuretics and even allopurinol.

Indications

Allopurinol is used to reduce urate concentrations in body fluids and/or urine to prevent or reverse the deposition of urate/uric acid and is indicated in the management of the main clinical manifestations of urate deposition which include chronic gouty arthritis, idiopathic gout and skin tophi.[2]

Mechanism of action

Allopurinol, and its active metabolite oxypurinol, both inhibit xanthine oxidase, an enzyme that converts hypoxanthine to xanthine, and xanthine to uric acid, thus decreasing the production of uric acid.[3] By lowering both serum and urine concentrations of uric acid below its solubility limits, allopurinol prevents or decreases urate deposition in the joints, thereby preventing the occurrence or progression of gouty arthritis.[4]

Pharmacokinetics

Around 80 to 90% of allopurinol is absorbed from the gastrointestinal tract following oral administration.[4] Seventy percent of allopurinol is metabolised in the liver and converted to oxypurinol by oxidative metabolism.[4] The half-life of allopurinol is one to three hours and for oxypurinol the half-life is around 15 hours (12–30 hours), and is prolonged in patients with impaired kidney function.[3,5] Oxypurinol, and up to 10% of unchanged allopurinol, is excreted in the urine.[5]

Dosing (adults)

Allopurinol treatment should be introduced at a low dosage of 100 mg/day to reduce the risk of adverse reactions such as nausea, vomiting and diarrhoea.[2] If needed, the dose may be increased by 100 mg/day every two to five weeks until the target serum uric acid level is achieved.[3] The usual maintenance dose is 300 mg/day. However, doses of up to 900 mg/day have been used.[2]

It is recommended that allopurinol be taken after meals for better gastrointestinal tolerability.[2,6]

Renal impairment

Allopurinol is excreted in the kidney and reduced renal function may lead to accumulation of the medicine and its metabolites. The dose and the frequency of dosing may therefore require reduction in these patients. The following schedule is recommended as guidance in adult patients with impaired renal function:[2]

Creatinine clearance > 20 ml/minute	give standard dose
Creatinine clearance between 10 and 20 ml/minute	give 100 to 200 mg/day
Creatinine clearance < 10 ml/minute	give 100 mg/day or at longer intervals.

If plasma monitoring facilities are available, plasma oxypurinol levels should be maintained below 100 micromol/litre (15,2 micrograms/mL).[2]

Allopurinol and its metabolites are removed by renal dialysis and dosages should be adjusted accordingly.[2]

Hepatic impairment

Reduced doses should be used in patients with hepatic impairment. Periodic liver function tests are recommended during the early stages of therapy.[2]

Efficacy

A 2014 Cochrane review reported that allopurinol 300 mg daily increases the proportion of patients achieving a target serum urate concentration (25/26 patients achieved target serum urate concentrations with allopurinol 300 mg daily compared to 0/26 with placebo).[7] A summary of two Cochrane reviews in 2014, concluded that there is moderate quality data supporting the efficacy and safety of allopurinol in gout.[8] Significantly more (38%) participants taking allopurinol, achieved a serum urate level of < 6.0 mg/dl when compared to placebo.[8]

S3

ALLOPURINOL 100 Cipla

Allopurinol 100 mg

S3

ALLOPURINOL 300 Cipla

Allopurinol 300 mg

Cipla

INDICATIONS[1]

ALLOPURINOL CIPLA is indicated for the treatment of gout and hyperuricaemia associated with other conditions.

It may be effective in patients with impaired renal function. ALLOPURINOL CIPLA is also used in the treatment of hyperuricaemia associated with leukaemia or resulting from radiotherapy or the use of antineoplastic agents such as mercaptopurine, or during treatment with diuretics of the thiazide or similar type.

S3 Reg. No. P/3.3/180, 181. Allopurinol 100 Cipla / Allopurinol 300 Cipla. Each tablet contains Allopurinol 100 mg / 300 mg. For full prescribing information, refer to the Professional Information approved by the medicines regulatory authority. References: 1. Professional Information approved by SAHPRA: Allopurinol 100 Cipla; Allopurinol 300 Cipla (Tablets). CIPLA MEDPRO (PTY) LTD. Co. Reg. No. 1995/004182/07. Building 9, Parc du Cap, Mispel Street, Bellville, 7530, RSA. Website: www.cipla.co.za. Customer Care: 080 222 6662 [1441517501a]

Safety

Contraindications

Allopurinol is contraindicated in patients with hypersensitivity to allopurinol or any excipients in the product, in patients with severe hepatic or renal disorders and in patients with an acute gout attack.[2]

Special warnings and precautions

Allopurinol should not be started until an acute attack of gout has completely subsided as further attacks may be precipitated by allopurinol.[2] Due to the destabilisation of intra-articular uric acid microtophi when initiating any urate-lowering therapy, there is an increased incidence of acute gouty flares, especially during the initial few months of allopurinol therapy.[3] Thus it is advisable to give a nonsteroidal anti-inflammatory drug (NSAID) or colchicine for at least one month when starting treatment with allopurinol.[2,6] If acute attacks occur in patients receiving allopurinol, treatment with allopurinol should continue at the same dose while the acute attack is treated with a NSAID or colchicine.[2]

If a skin rash or other signs of hypersensitivity occur, treatment with allopurinol should be withdrawn immediately as this could result in more serious hypersensitivity reactions including Stevens-Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN) and drug rash with eosinophilia and systemic symptoms (DRESS). After recovery from mild symptoms, allopurinol may be reintroduced at a low dose (e.g. 50 mg per day) and gradually increased. If the rash recurs, allopurinol should be permanently withdrawn.[2]

Certain populations (including people of Han Chinese, African and Indian ancestry) carry the HLAB-B*5801 allele which is considered a genetic risk factor for serious hypersensitivity reactions (e.g. SJS/TEN) with allopurinol use. Screening of these high-risk patients should be considered before starting treatment with allopurinol. Those individuals who test positive should not start treatment with allopurinol unless there are no other reasonable therapeutic options and the benefits of use outweigh the potential associated risk. Those who test negative may still be at risk of SJS/TEN.[2]

Drug interactions

Allopurinol may increase the activity of certain medications. When using 6-mercaptopurine or azathioprine with allopurinol, the dose of 6-mercaptopurine or azathioprine should be reduced to a quarter of the usual dose.[2,6] Theophylline metabolism may be inhibited, and theophylline levels should be monitored in patients starting or increasing allopurinol therapy. Plasma concentration of ciclosporin may be increased and ciclosporin toxicity should be considered if used with allopurinol.

Medicines with uricosuric activity such as probenecid or large doses of salicylate may accelerate the excretion of oxypurinol which may reduce the efficacy of allopurinol.[6]

Concomitant use of allopurinol and ampicillin or amoxicillin may increase the risk of developing a skin rash. When possible, an alternative to ampicillin or amoxicillin should be considered in patients using allopurinol.[6]

Please refer to the manufacturer's professional information for further information on possible drug-drug interactions.

Adverse effects

The most common adverse effects associated with the use of allopurinol include maculopapular pruritic rash, nausea and vomiting.[3] Gastrointestinal side effects can be reduced by taking allopurinol with plenty of liquids and by having frequent small meals.[9] Other adverse effects include altered taste, drowsiness and diarrhoea.

Less commonly, allopurinol can cause a rash or flaking of the skin. Patients should stop treatment if a rash develops, especially if it is a severe skin rash or, in rare instances, if mouth ulceration occurs.[9] Other less common and rare side-effects include liver necrosis, granulomatous hepatitis, cholestatic jaundice, interstitial nephritis, and vasculitis.

Important prescribing points

- Allopurinol should not be initiated until an acute attack of gout has completely subsided. There is an increased incidence of acute gouty flares, especially during the initial few months when starting treatment.[3] Thus, it is advisable to give an NSAID or colchicine concurrently with allopurinol for at least one to six months when starting treatment.[2,9]
- A high fluid intake and frequent small meals may reduce the incidence of nausea and vomiting associated with allopurinol therapy.[9]
- Patients should be warned that drowsiness, vertigo and ataxia may occur and should exercise caution when driving, using machinery or participating in dangerous activities.[5,6]
- A doctor should be consulted if a skin rash or any other sign of hypersensitivity occurs.[2,5]

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Prostate safety events during testosterone replacement therapy in men with hypogonadism - a randomized clinical trial

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Importance: The effect of testosterone replacement therapy (TRT) on the risk of prostate cancer and other adverse prostate events is unknown.

Objective: To compare the effect of TRT vs placebo on the incidences of high-grade prostate cancers (Gleason score >4 + 3), any prostate cancer, acute urinary retention, invasive prostate procedures, and pharmacologic treatment for lower urinary tract symptoms in men with hypogonadism.

Design, setting, and participants: This placebo-controlled, double-blind randomized clinical trial enrolled 5246 men (aged 45-80 years) from 316 US trial sites who had 2 testosterone concentrations less than 300 ng/dL, hypogonadal symptoms, and cardiovascular disease (CVD) or increased CVD risk. Men with prostate-specific antigen (PSA) concentrations greater than 3.0 ng/mL and International Prostate Symptom Score (IPSS) greater than 19 were excluded. Enrollment took place between May 23, 2018, and February 1, 2022, and end-of-study visits were conducted between May 31, 2022, and January 19, 2023.

Intervention: Participants were randomized, with stratification for prior CVD, to topical 1.62% testosterone gel or placebo.

Main outcomes and measures: The primary prostate safety end point was the incidence of adjudicated high-grade prostate cancer. Secondary end points included incidence of any adjudicated prostate cancer, acute urinary retention, invasive prostate surgical procedure, prostate biopsy, and new pharmacologic treatment. Intervention effect was analyzed using a discrete-time proportional hazards model.

Results: A total of 5204 men (mean [SD] age, 63.3 [7.9] years) were analyzed. At baseline, the mean (SD) PSA concentration was 0.92 (0.67) ng/mL, and the mean (SD) IPSS was 7.1 (5.6). The mean (SD) treatment duration as 21.8 (14.2) months in the TRT group and 21.6 (14.0) months in the placebo group. During 14 304 person-years of follow-up, the incidence of high-grade prostate cancer (5 of 2 596 [0.19%] in the TRT group vs 3 of 2 602 [0.12%] in the placebo group; hazard ratio, 1.62; 95% CI, 0.39-6.77; $p = .51$) did not differ significantly between groups; the incidences of any prostate cancer, acute urinary retention, invasive surgical procedures, prostate biopsy, and new pharmacologic treatment also did not differ significantly. Change in IPSS did not differ between groups. The PSA concentrations increased more in testosterone-treated than placebo-treated men.

Conclusions and relevance: In a population of middle-aged and older men with hypogonadism, carefully evaluated to exclude those at high risk of prostate cancer, the incidences of high-grade or any prostate cancer and other prostate events were low and did not differ significantly between testosterone- and placebo-treated men. The study's findings may facilitate a more informed appraisal of the potential risks of TRT.

Trial registration: ClinicalTrials.gov Identifier: NCT03518034

Republished with permission: *JAMA Network Open*. 2023;6(12):e2348692. 10.1001/jamanetworkopen.2023.48692

Key Points

Question: Does testosterone replacement therapy in men with hypogonadism increase the risk of high- grade or any prostate cancer or other adverse prostate events?

Findings: During 14 304 person-years of follow-up of 5 204 men (aged 45–80 years) with hypogonadism in this randomized clinical trial, incidences of high-grade or any prostate cancer, acute urinary retention, invasive surgical procedures, and new pharmacologic treatment were low and did not differ significantly between groups.

Meaning: The study's findings will facilitate a more informed appraisal of the potential prostate risks of testosterone replacement therapy.

Introduction

The relationship between testosterone replacement therapy (TRT) and the risk of prostate cancer remains incompletely studied.[1-3] Epidemiologic studies have not found a consistent association between prostate cancer risk and testosterone levels or polymorphisms in genes involved in androgen action.[4-13] Prostate events were not adjudicated in any testosterone trial, and none have reported the incidence of high-grade prostate cancer or other prostate events, such as acute urinary retention, invasive prostate procedures, or initiation of new pharmacologic therapy for benign prostatic hyperplasia (BPH).[1,14] Because of uncertainty about the risk of prostate events during TRT, most professional society guidelines recommend against TRT in men with a history or increased risk of prostate cancer.[1,2,15]

In 2015, the US Food and Drug Administration required testosterone manufacturers to conduct a randomized clinical trial to determine the effect of TRT on major adverse cardiovascular events (MACEs).[16] The Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) study was designed to meet this regulatory requirement.[17] Because of its large size and longer duration, the TRAVERSE study offered a unique opportunity to evaluate the effects of TRT on prostate safety events.[17] The study compared the effects of TRT and placebo on the incidences of high-grade prostate cancer, any prostate cancer, acute urinary retention, invasive prostate surgical procedures for BPH, and initiation of pharmacologic therapy for BPH. Prostate events were recorded using a structured protocol and adjudicated. To minimize ascertainment bias due to greater likelihood of urologic referral for prostate biopsy because of testosterone-induced elevation in prostate-specific antigen (PSA) concentrations, the TRAVERSE study protocol prespecified procedures for managing PSA elevations and urologic referrals.

Methods

This randomized clinical trial's design, as well as the MACEs and overall safety results, have been previously published.[17,18] Briefly, this placebo-controlled, double-blind, parallel-group randomized clinical trial enrolled men, aged 45–80 years, with 2 fasting, morning testosterone concentrations, measured using liquid chromatography–tandem mass spectrometry, less than 300 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) in a central laboratory certified by the Hormone Standardization Program for Testosterone, 1 or more symptoms of hypogonadism, and prior cardiovascular disease (CVD) or increased risk of CVD.[17] Men with history of prostate cancer, PSA concentrations greater than 3.0 ng/mL (or >1.5 ng/mL if receiving a steroid 5α-reductase inhibitor [5ARI] [to convert to micrograms per liter, multiply by 1]), severe lower urinary tract symptoms (LUTSs) (International Prostate Symptom Score [IPSS] >19), or a prostate nodule or induration were excluded. A PSA cutoff of 3 ng/mL was established to exclude men at increased prostate cancer risk.[19] Participants were randomized in a 1:1 ratio with stratification for preexisting CVD to receive 1.62% transdermal testosterone gel or matching placebo gel for the duration of the study. Testosterone dose was adjusted, while maintaining blinding, based on on-treatment testosterone and hematocrit levels to maintain testosterone concentrations between 350 and 750 ng/dL and hematocrit levels less than 54% (to convert to a proportion of 1.0, multiply by 0.01).[17,18] Participants' self-reported race and ethnicity were collected because racial differences in the incidence of clinical prostate cancers are well recognized. The trial was conducted at 316 US sites. Enrollment took place between May 23, 2018, and February 1, 2022, and end-of-study visits were conducted between May 31, 2022, and January 19, 2023. The study protocol was approved by the national and local institutional review boards for human subjects research. All participants provided written informed consent. An independent data and safety monitoring board reviewed safety data every 6 months.

Prostate safety monitoring plan

The prespecified prostate safety monitoring plan is provided in Supplement 1. The PSA levels were measured at baseline, 3 months, 12 months, and annually thereafter, and IPSS was assessed at baseline, 3 months, 12 months, 36 months, and the end of the study. Digital prostate examinations were performed at baseline, 12 months, 36 months, and end of study. At each visit, participants were asked structured questions about LUTS and prostate procedures. If a prostate procedure was reported, an attempt was made to obtain pathology reports and tissue.

To minimize the ascertainment bias attributable to the increased risk of being referred for a prostate biopsy because of testosterone-induced increase in PSA levels, the criteria for urologic referral were prespecified. The participants were referred for urologic evaluation and possible biopsy if they had any of the following: (1) confirmed PSA increase more than 1.4 ng/mL above baseline in the first year of treatment (or >0.7 ng/mL in 5ARI-treated men); (2) confirmed PSA concentration greater than 4.0 ng/mL at any time (>2.0 ng/mL in 5ARI-treated men); (3) for men aged 45 to 54 years with a baseline PSA concentration less than 1.5 ng/mL, a PSA level increasing to 3.0 ng/mL at any time (<0.75 ng/mL increasing to 1.5 ng/mL for 5ARI-treated men); or (4) prostate nodule or induration at any time. For criteria 1, 2, and 3, elevations in PSA concentrations were confirmed by repeating the test.[20,21] For the men who met these criteria, prostate cancer risk was estimated using the Prostate Cancer Prevention Trial Risk Calculator, version 2.0 (UT Health San Antonio), and participants were provided an institutional review

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Indication: [1]

- Testosterone replacement therapy for male hypogonadism in adult men when testosterone deficiency has been confirmed by clinical features and biochemical tests

Pharmacokinetic properties:[1]

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In men with hypogonadism Androgel® is associated with a range of benefits such as: [2,3,4]

- Improved mood
- Improved libido and sexual function
- Improved metabolic parameters
- Increased lean muscle mass
- Reduced body fat mass

Androgel® has been shown to significantly improve overall health-related quality of life in men with low testosterone.[4]

A40/21.7/0260

Nappi Code	Medicine Schedule	Active ingredient	Strength	Dosage Form	Quantity
3000765-001	S5	Testosterone	50mg/5g	Gel in sachet	30 per box

References: 1. **Androgel®** Package Insert; 2. Wang C et al.J Clinc Endocrinol Metab 2000;85:2839-2853; 3. Wang C et al.J Clinc Endocril Metab 2004;89:2085-2098; 4. Behre HM et al.Aging Male 2013;15:198-207

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board–approved video that described the potential benefits and risks of prostate biopsy[22] to facilitate informed decision-making regarding prostate biopsy.

Prostate safety end points

The primary prostate safety end point was the incidence of high-grade prostate cancer (Gleason score 4 + 3 or higher). Secondary end points included the incidence of any prostate cancer, acute urinary retention, invasive prostate surgical procedure for BPH, prostate biopsy, and new pharmacologic treatment for LUTSs. The LUTSs were evaluated using the IPSS. Changes in PSA concentrations from baseline and from month 12 were determined.

Adjudication of prostate safety end points

A blinded Prostate Adjudication Committee adjudicated prostate cancer diagnosis and Gleason score, acute urinary retention, and invasive prostate surgical procedure for BPH. The diagnosis of prostate cancer was based on evaluation of tissue from prostate biopsy specimens and surgical procedures by the Prostate Adjudication Center at the University of Colorado. If tissue or slides were not available, the Prostate Adjudication Committee reviewed site pathology reports. High-grade prostate cancer was defined as a Gleason score of 4 + 3 or higher.[23] Acute urinary retention was defined as inability to voluntarily pass urine, requiring a visit to the emergency department, and/or placement of a catheter, ascertained by participant self-report and verified by medical record. An invasive prostate procedure was defined as any surgical procedure for BPH other than a prostate biopsy, verified by medical record.

Statistical analysis

The trial's statistical analysis plan is available in Supplement 2. Analyses used SAS software, version 9.4 (SAS Institute Inc) and R, version 4.2.1 (R Foundation for Statistical Computing).[24] Descriptive analyses of baseline characteristics were conducted in the full analysis set, which included all randomized participants. Prostate safety analyses were conducted in the safety set, which included all randomized participants who received at least 1 dose of the study drug. The data analysis and interpretation of the data were performed by the statisticians associated with the Prostate Substudy Committee (K.B., K.M.P., and T.G.T.).

Analysis of the primary safety end point and event-based secondary end points used a discrete- time proportional hazards model[25] with event intervals based on scheduled visits. All postrandomization events were included. Hazard ratios (HRs) for treatment effect and associated 95% CIs and Wald *P*-values were calculated, adjusting for prior CVD. The discrete-time model was prespecified under the assumption that exact event times might not be consistently available for analysis during the COVID-19 pandemic, a concern that proved unfounded, so an additional post hoc Cox proportional hazards analysis using actual time of events was conducted. Aalen-Johansen estimates of cumulative incidence of prostate events with death as a competing risk were calculated. Post hoc sensitivity analyses of events occurring within 1 year and within 30 days of the last dose of the study drug were also conducted.

Changes over time in IPSSs, PSA levels, and hormone levels were analyzed using linear mixed- effects models with fixed effects for treatment, visit, treatment × visit interaction, baseline value, CVD status, and a random-subject effect using an unstructured covariance. Least-squares means estimates, 95% CIs, and *P*-values for treatment effect were computed using an *F* test. For PSA, a mixed model was used to test whether treatment difference continued to increase after month 12 by comparing month 12 with the mean of later visits. All hypothesis tests used a 2-sided significance level of $p < .05$.

The study was powered to establish noninferiority for the MACE end point within a noninferiority margin of an upper confidence limit of the HR less than 1.5. Approximately 6 000 individuals were to be recruited to accrue 256 MACEs (90% power) under the initial assumptions of annual event rate, accrual rate, and discontinuation rate.[17]

Results

Among 32 152 screened men, 50 (0.16%) were excluded because of a history of prostate or breast cancer, 1201 (3.74%) for PSA concentrations greater than 3.0 ng/mL (or >1.5 ng/mL if receiving 5ARIs), 549 (1.71%) for IPSSs greater than 19, and 57 (0.18%) for prostate nodule or induration; these percentages should be interpreted with caution because men who failed screening at earlier screening visits did not complete subsequent screening assessments. Among 5 246 identification numbers of randomized men, 42 were attributed to 20 participants with duplicate enrollment. After excluding these duplicates, the full analysis set included 5204 participants (mean [SD] age, 63.3 [7.9] years; self-reported race: 877 [16.9%] Black, 4 154 [79.8%] White, and 173 [3.3%] other; self- reported Hispanic or Latinx ethnicity, 848 [16.3%]), with 2 601 in the TRT group and 2 603 in the placebo group. The safety set included 5198 participants (2 596 in the TRT group and 2602 in the placebo group) who received at least 1 dose of study medication (**Figure 1**).

As reported earlier,[18] the mean (SD) follow-up duration was 33.0 (12.1) months. Of 5 204 participants in the full analysis set, 4 804 (92.3%) were followed up for at least 1 one year, 3 842 (73.9%) for 2 years, 2974 (57.2%) for 3 years, and 85 (1.6%) for 4 years, yielding 14 304 person-years of follow-up. The mean (SD) treatment duration was 21.8 (14.2) months in the TRT group and 21.6 (14.0) months in the placebo group, and treatment discontinuation rates were similar between the 2 arms.

Baseline characteristics of the participants have been previously published.[18] The mean (SD) PSA concentration was 0.92 (0.67) ng/mL. Of 5 182 men with nonmissing baseline PSA values, 3 347 (64.6%) had PSA concentrations less than 1 ng/mL, 1 355 (26.1%) had PSA concentrations between 1.00 and 1.99 ng/mL, and 480 (9.3%) had PSA concentrations between 2 and 3 ng/mL. The mean (SD) baseline IPSS was 7.1 (5.6).

High-grade and all prostate cancers

As reported previously in the trial's overall safety events,[18] during 14 304 person-years of follow-up, there were 5 participants with high-grade prostate cancer in the TRT group and 3 in the placebo group. The incidence of high-grade prostate cancer did not differ significantly between groups (5 of 2 596 [0.19%] in the TRT group vs 3 of 2 602 [0.12%] in the placebo group; hazard ratio, 1.62; 95% CI, 0.39-6.77; $p = .51$) (Figure 2 and Figure 3). Among the 8 participants with high-grade cancer, 3 had baseline PSA concentrations between 1 and 1.99 ng/mL and 5 between 2 and 3 ng/mL.

The number of participants with any prostate cancer did not differ between the TRT (12 [0.46%]) and placebo (11 [0.42%]) groups (HR, 1.07; 95% CI, 0.47-2.42; $p = .87$). Among 23 men with prostate cancer, 1 had a baseline PSA concentration less than 1 ng/mL, 8 between 1 and 1.99 ng/mL, and 14 between 2 and 3 ng/mL. The highest postbaseline PSA concentration before biopsy in these 23 men is shown in eTable 1 in Supplement 3.

Other secondary prostate safety end points

Twenty testosterone-treated men (0.77%) and 16 placebo-treated men (0.61%) developed acute urinary retention, with no significant difference between groups (HR, 1.25; 95% CI, 0.65-2.41; $p = .50$). Twenty-three men (0.89%) in the TRT group underwent an invasive surgical prostate procedure compared with 12 (0.46%) in the placebo group (HR, 1.91; 95% CI, 0.95-3.84; $p = .07$). Rates of new pharmacologic therapy for LUTSs did not differ significantly between the TRT and placebo groups (101 [3.89%] vs 87 [3.34%]; HR, 1.16; 95% CI, 0.87-1.54; $p = .32$) (Figure 2 and Figure 3).

Eighty-five men (1.6%) met the criteria for referral for urologic evaluation, 57 (2.2%) in the TRT group vs 28 (1.1%) in the placebo group. Sixty men (39 in the TRT group and 21 in the placebo group) had confirmed PSA concentrations greater than 4.0 ng/mL, 37 men (25 in the TRT group and 12 in the placebo group) had confirmed increases in PSA concentrations greater than 1.4 ng/mL above baseline during the first year (or >0.7 ng/mL for those taking 5ARIs), 5 men (4 in the TRT group and 1 in the placebo group) had a new

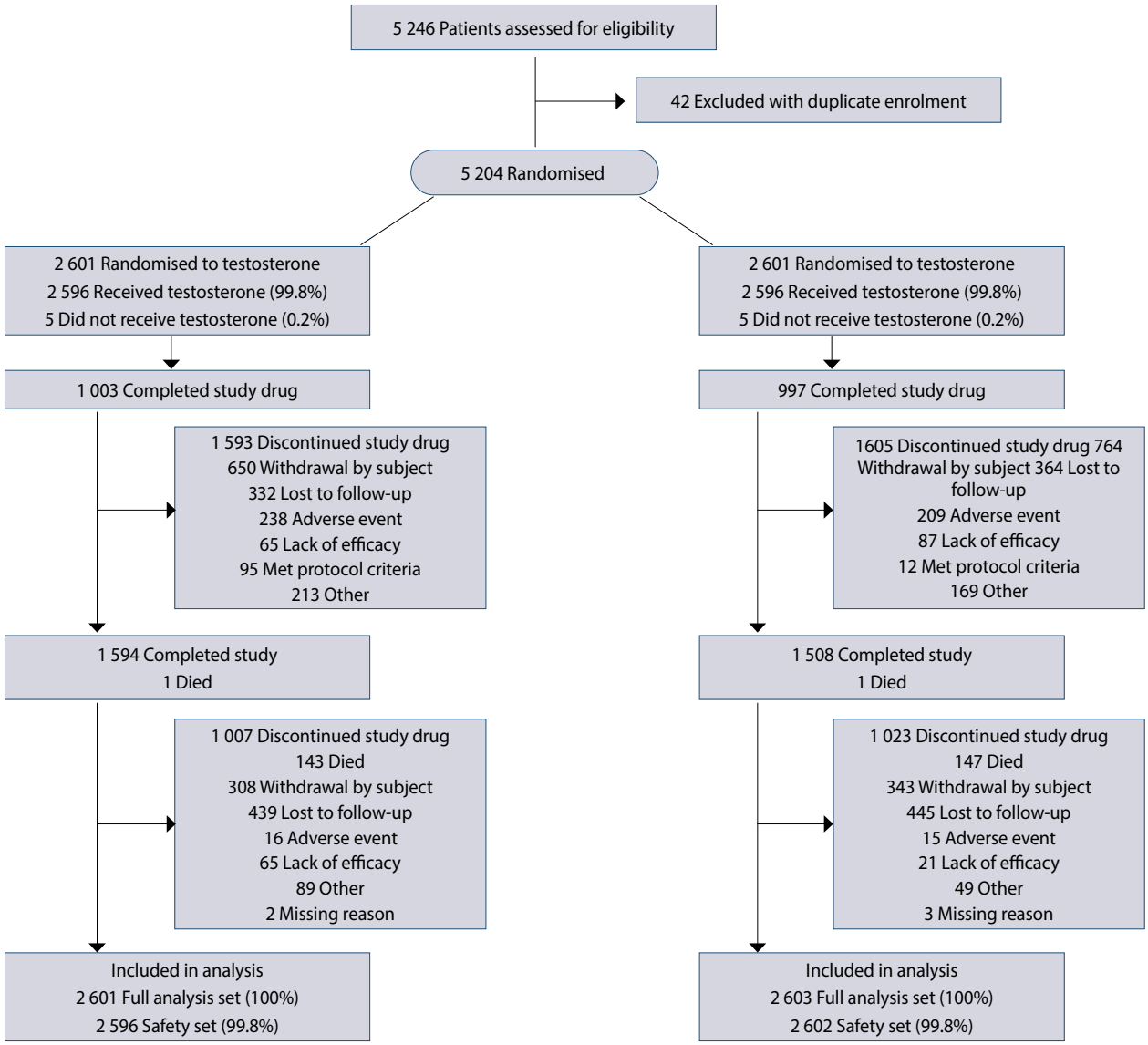
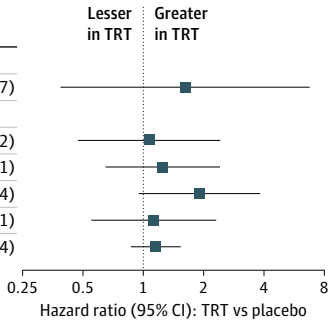


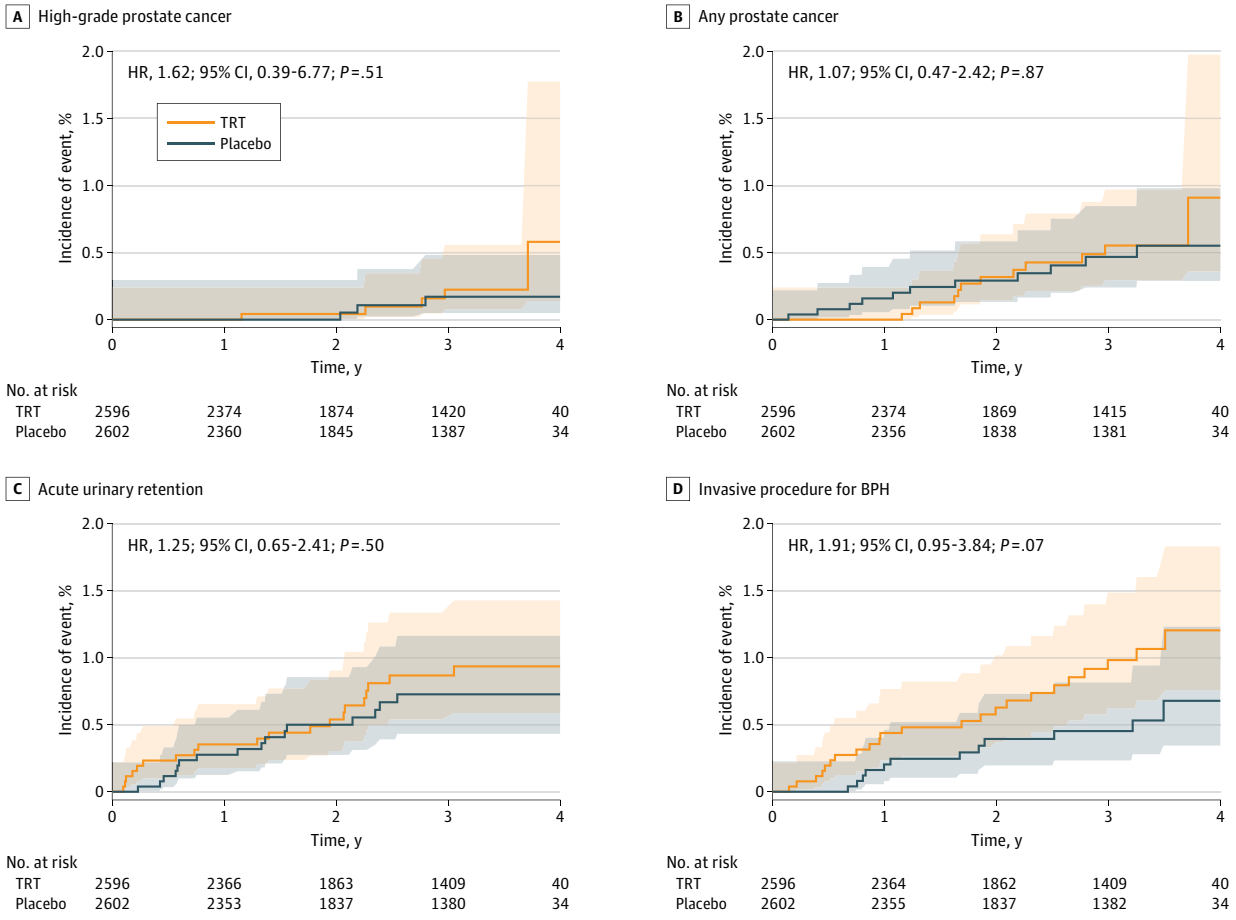
Figure 1: CONSORT flow diagram

End point	No. (%) participants experiencing events: TRT (*n* = 2596)	Placebo (*n* = 2602)	Hazard ratio (95% CI): TRT vs placebo
Primary			
High-grade prostate cancer	5 (0.19)	3 (0.12)	1.62 (0.39-6.77)
Secondary			
Any prostate cancer	12 (0.46)	11 (0.42)	1.07 (0.47-2.42)
Acute urinary retention	20 (0.77)	16 (0.61)	1.25 (0.65-2.41)
Invasive procedure for BPH	23 (0.89)	12 (0.46)	1.91 (0.95-3.84)
Prostate biopsy	16 (0.62)	14 (0.54)	1.13 (0.55-2.31)
New pharmacologic treatment	101 (3.89)	87 (3.34)	1.16 (0.87-1.54)



Discrete-time proportional hazards model estimates of hazard ratios (95% CIs) quantifying differential risk in testosterone replacement therapy (TRT) relative to placebo are shown in the forest plot. The hazard ratios are the hazard in the TRT group over the hazard in the placebo group, so a value greater than 1 indicates an excess of prostate events in the TRT group. BPH indicates benign hyperplasia.

Figure 2: Incidence of primary (High-grade prostate cancer) and secondary prostate safety end points



Aalen-Johansen estimates of cumulative incidence with death as a competing risk, together with pointwise 95% CIs, are shown. Hazard ratios (HRs) and associated 95% CIs and P values based on the discrete proportional hazards model are also shown.

Between-group differences are not statistically significant. BPH indicates benign prostatic hyperplasia; HR, hazard ratio; and TRT, testosterone replacement therapy.

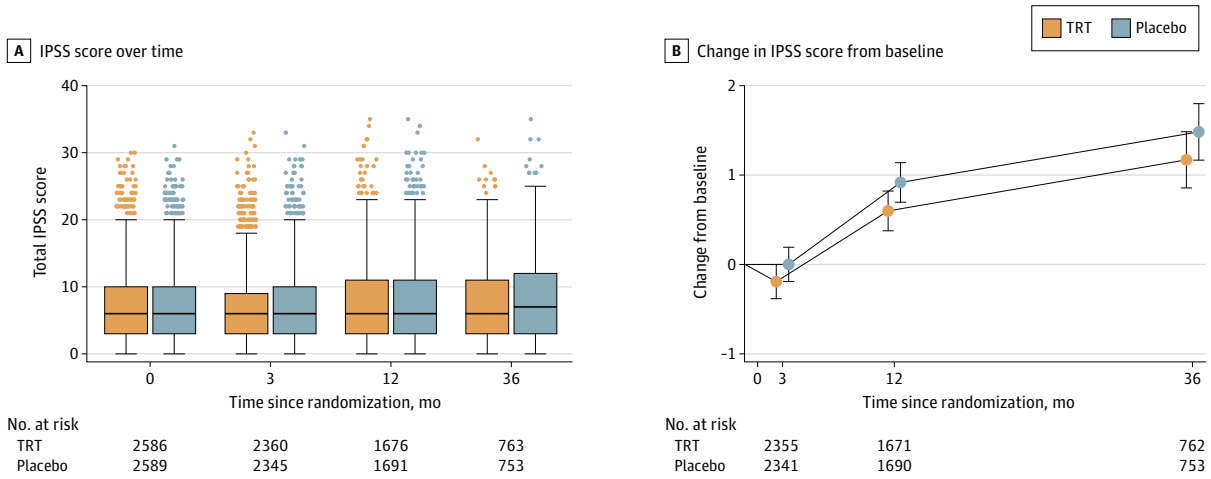
Figure 3: Estimated cumulative incidences of primary and secondary event-based outcomes as a function of time from baseline

prostate nodule or induration, and 1 man (in the TRT group) had a PSA concentration that increased from less than 1.5 ng/mL at baseline to greater than 3.0 ng/mL.

Of the 85 men who met the criteria for urologic referral, 16 (18.8%) elected to undergo prostate biopsy; an additional 14 men who did not meet these criteria also underwent biopsy. The numbers of prostate biopsies (16 in the TRT group vs 14 in the placebo group) did not differ between groups (0.62% vs 0.54%; HR, 1.13; 95% CI, 0.55-2.31; p = .74). Eighteen men who underwent biopsy had baseline PSA concentrations between 2 and 3 ng/mL.

Post Hoc Sensitivity Analyses

Post hoc analysis for primary and secondary event end points using a Cox proportional hazards regression model (Figure 1 in Supplement 3) yielded results similar to those of prespecified



The lower urinary tract symptoms were evaluated using the International Prostate Symptom Score (IPSS). TRT indicates testosterone replacement therapy.

Figure 4: Changes in lower urinary tract symptoms over time

Table: Change from baseline in serum PSA levels in study participants categorized by baseline PSA levels

Treatment	No.	PSA level, mean (SD)	Change from baseline, least-squares mean (95% CI)	Treatment difference, least-squares mean (95% CI)
Baseline PSA <1 ng/mL				
Month 0				
TRT	1572	0.51 (0.24)	NA	NA
Placebo	1549	0.51 (0.24)	NA	NA
Month 3				
TRT	1557	0.65 (0.48)	0.14 (0.10 to 0.18)	0.07 (0.01 to 0.12)
Placebo	1529	0.59 (0.63)	0.07 (0.03 to 0.11)	NA
Month 12				
TRT	1122	0.71 (0.68)	0.19 (0.15 to 0.24)	0.06 (–0.01 to 0.12)
Placebo	1075	0.65 (1.42)	0.14 (0.09 to 0.19)	NA
Month 24				
TRT	762	0.72 (0.84)	0.20 (0.15 to 0.26)	0.13 (0.05 to 0.21)
Placebo	696	0.59 (0.48)	0.08 (0.02 to 0.13)	NA
Month 36				
TRT	446	0.72 (0.67)	0.20 (0.12 to 0.27)	–0.02 (–0.12 to 0.08)
Placebo	432	0.74 (1.26)	0.22 (0.15 to 0.29)	NA
Month 48				
TRT	128	0.74 (0.49)	0.21 (0.08 to 0.34)	–0.03 (–0.22 to 0.15)
Placebo	119	0.83 (1.64)	0.24 (0.11 to 0.38)	NA
Baseline PSA 1 to <2 ng/mL				
Month 0				
TRT	642	1.40 (0.28)	NA	NA
Placebo	630	1.39 (0.28)	NA	NA
Month 3				
TRT	635	1.64 (0.82)	0.24 (0.17 to 0.30)	0.18 (0.09 to 0.28)
Placebo	624	1.44 (0.96)	0.05 (–0.01 to 0.12)	NA
Month 12				
TRT	454	1.65 (0.87)	0.26 (0.18 to 0.33)	0.26 (0.16 to 0.37)
Placebo	478	1.38 (0.64)	–0.01 (–0.08 to 0.07)	NA
Month 24				
TRT	338	1.60 (0.93)	0.20 (0.11 to 0.28)	0.18 (0.06 to 0.30)
Placebo	307	1.38 (0.76)	0.02 (–0.07 to 0.11)	NA

Table: Change from baseline in serum PSA levels in study participants categorized by baseline PSA levels

Treatment	No.	PSA level, mean (SD)	Change from baseline, least-squares mean (95% CI)	Treatment difference, least-squares mean (95% CI)
Month 36				
TRT	230	1.68 (0.95)	0.27 (0.17 to 0.37)	0.10 (–0.05 to 0.24)
Placebo	213	1.51 (1.14)	0.17 (0.07 to 0.28)	NA
Month 48				
TRT	74	1.75 (0.85)	0.36 (0.19 to 0.53)	0.10 (–0.16 to 0.37)
Placebo	51	1.68 (0.90)	0.25 (0.05 to 0.45)	NA
Baseline PSA 2-3 ng/mL				
Month 0				
TRT	195	2.46 (0.28)	NA	NA
Placebo	251	2.43 (0.30)	NA	NA
Month 4				
TRT	192	2.74 (1.09)	0.29 (–0.02 to 0.60)	0.20 (–0.21 to 0.62)
Placebo	250	2.52 (1.95)	0.08 (–0.19 to 0.36)	NA
Month 12				
TRT	146	2.91 (1.22)	0.46 (0.10 to 0.81)	0.45 (–0.03 to 0.93)
Placebo	176	2.43 (1.33)	0.01 (–0.32 to 0.33)	NA
Month 24				
TRT	93	2.97 (3.29)	0.59 (0.15 to 1.03)	0.06 (–0.53 to 0.66)
Placebo	112	2.90 (4.91)	0.53 (0.13 to 0.93)	NA
Month 36				
TRT	60	2.74 (1.03)	0.29 (–0.25 to 0.83)	0.21 (–0.52 to 0.94)
Placebo	72	2.14 (1.05)	0.08 (–0.41 to 0.57)	NA
Month 48				
TRT	17	3.11 (1.44)	0.52 (–0.48 to 1.52)	0.51 (–0.78 to 1.80)
Placebo	25	2.24 (0.97)	0.01 (–0.81 to 0.83)	NA

analyses. Similarly, the results of the sensitivity analyses in which events 1 year and 30 days after the end of treatment were censored (eFigures 2 and 3 in Supplement 3) were similar to those of prespecified analyses.

Lower Urinary Tract Symptoms

The IPSS increased over time in both groups (Figure 4); change from baseline in IPSS did not differ significantly between groups. Of 4809 men with any postbaseline IPSS, 378 (7.9%) had a score greater than 19 (180 [7.5%] in the TRT group and 198 [8.2%] in the placebo group).

PSA levels

Testosterone treatment was associated with a greater increase in PSA levels than placebo (estimated between-group difference, 0.11 [95% CI, 0.07-0.15] ng/mL at 3 months; 0.15 [95% CI, 0.08-0.21] ng/mL at 12 months; 0.11 [95% CI, –0.01 to 0.21] ng/mL at 24 months; 0.01 [95% CI, –0.09 to 0.10] ng/mL at 36 months; and 0.09 [95% CI, –0.04 to 0.22] ng/mL at 48 months; omnibus test $p < .001$) (eFigure 4 in Supplement 3) regardless of baseline PSA concentration (Table). There was no significant between-group difference in PSA levels after month 12; the difference at time points after month 12 was significantly smaller than difference at month 12.

Hormone levels

Mean (SD) total testosterone was 220 (48) ng/dL at baseline.[18] As reported, testosterone and estradiol levels,[18] as well as dihydrotestosterone levels (eTable 2 in Supplement 3), increased significantly in testosterone-treated men but did not change in placebo-treated men.

Discussion

The TRAVERSE study is, to our knowledge, the largest randomized trial of TRT conducted to date, with prospectively recorded and adjudicated prostate safety outcomes. Among middle-aged and older men with hypogonadism who had or were at increased risk of CVD, the incidence of high-grade or any prostate cancer in TRT-treated men with a baseline PSA concentration less than 3.0 ng/mL was low and not significantly different from that in placebo-treated men. This group of men whose PSA concentration is less than 3.0 ng/mL represents most of the aging US population.[26] Similarly, incidences of acute urinary retention, invasive surgical procedure for BPH, or new pharmacologic treatment for LUTSs did not differ between the treatment groups. The invasive prostate surgical

procedures were more common in the TRT group compared with the placebo group, although the difference was not significant. Consistent with meta-analyses of smaller testosterone trials, TRT did not increase IPSSs.[14,27] Although PSA concentrations increased more among the TRT group than the placebo group, the mean increase was small and between-group difference did not widen after 12 months. Thus, in a population men with hypogonadism and PSA concentrations less than 3 ng/mL who were evaluated carefully to exclude those at increased prostate cancer risk, TRT was associated with low risk of adverse prostate events, including cancer.

Prostate cancer is highly prevalent among older men, but only a small fraction have high-grade tumors.[19] Androgen receptor signaling plays a central role in prostate cancer biology, and testosterone treatment promotes the growth of metastatic prostate cancer.[28] A mendelian randomization analysis found an increased incidence of prostate cancer in men with higher genetically determined testosterone level[29]; conversely, men with Klinefelter syndrome have lower risk of prostate cancer.[30] These data have led to concerns that TRT could promote progression of subclinical low-grade prostate cancer.[1] Because TRT increases PSA in men with hypogonadism, PSA elevations in older men receiving TRT could lead to prostate biopsy and detection of a subclinical low-grade prostate cancer.[1] To minimize the risk of unnecessary prostate biopsies and mitigate ascertainment bias, while enabling detection of prostate cancers for which clinical management may reduce long-term disease-related morbidity and mortality, the study protocol specified PSA elevation thresholds for referral to a urologist.[21,31] Elevations in PSA concentrations above these thresholds were verified, and participants with confirmed PSA elevation were asked to watch a video on the significance of PSA elevation and the benefits and risks of prostate biopsy to facilitate a shared decision on prostate biopsy. This approach was effective in reducing the number of prostate biopsies in both treatment groups; the small number of biopsies and high percentage of positive biopsy results in the trial support its usefulness in facilitating shared decision-making before prostate biopsy in men receiving TRT.

Limitations

The trial has some limitations. These findings should not be applied to patients with known prostate cancer, those with higher PSA values, or men who do not have confirmed hypogonadism. Although the TRAVERSE study was longer than most other randomized clinical trials of TRT, carcinogens may require many years to induce malignant neoplasms. The trial's structured evaluation of men after PSA testing did not include prostate imaging or other biomarker tests that may influence the decision to perform a biopsy. It is possible that shared decision-making played a role in lower rates of prostate biopsy; results could be different in a setting in which shared decision-making is not made available. Although the trial's sample size is the largest of any randomized testosterone trials to date, the numbers and incidences of any prostate cancer and high-grade prostate cancer were low. Because of the small number of prostate cancer events, these findings should not be interpreted to imply that the risk of prostate cancer in the testosterone and placebo groups was similar. The trial's findings indicate that in men with hypogonadism who were screened and monitored carefully using a structured protocol, the risk of high-grade or any prostate cancer and other prostate events is low. The trial's findings do not apply to men at high risk of prostate cancer, who were excluded. Rates of study medication discontinuation and loss to follow-up were high, although not dissimilar from those in randomized trials in other symptomatic conditions[32,33] or in hypogonadal men prescribed TRT.[34] The trial was conducted during the COVID-19 pandemic, which affected retention. However, nonretention rates were similar in the 2 groups. Among participants who discontinued trial participation, nearly half did so after end-of-study visits had started, and findings were similar in sensitivity analyses limited to follow-up durations of 1 month or 1 year after the last administered dose. The study population met the Endocrine Society's criteria for hypogonadism[1] but had high rates of diabetes, obesity, and other comorbid conditions, not dissimilar from men with hypogonadism[35] receiving TRT in the US.[36]

Conclusions

In this randomized clinical trial of men with hypogonadism who were carefully evaluated to exclude those at high risk for prostate cancer and followed using a standardized monitoring plan, TRT was associated with low and similar incidences of high grade or any prostate cancer, acute urinary retention, and invasive surgical procedures for BPH compared with a placebo. Testosterone replacement therapy did not worsen LUTSs. The concern about prostate risk heavily influences decision-making by clinicians and patients who are considering TRT for hypogonadism. The study's findings will facilitate a more informed appraisal of the potential risks of TRT.

Author contributions

Drs Bhasin and Buhr had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Travison and Pencina contributed equally to this work.

Concept and design

Bhasin, Travison, Pencina, Cunningham, Nissen, Snabes, Tangen, Thompson.

Acquisition, analysis, or interpretation of data

Bhasin, Travison, Pencina, O'Leary, Lincoff, Nissen, Lucia, Preston, Khera, Khan, Li, Tangen, Buhr, Thompson.

Drafting of the manuscript

Bhasin, Pencina, Cunningham, Preston, Thompson.

Critical review of the manuscript for important intellectual content

Bhasin, Travison, Pencina, O'Leary, Lincoff, Nissen, Lucia, Khera, Khan, Snabes, Li, Tangen, Buhr.

Statistical analysis

Bhasin, Travison, Pencina, O'Leary, Li, Tangen, Buhr.

Obtained funding

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Administrative, technical, or material support

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Supervision

Bhasin, Travison, O'Leary, Thompson.

Wrote protocol drafts for original protocol

Snabes.

Conflict of interest disclosures

Dr Bhasin reported receiving grants from Metri International Biotech and Function Promoting Therapies and consulting fees from OPKO and Versanis outside the submitted work; in addition, Dr Bhasin holds a patent as a co-inventor of a method for free testosterone measurement. Dr Lincoff reported receiving grants from Esperion, Commonwealth Serum Laboratories, Ltd., Novartis, and AstraZeneca; personal fees from Eli Lilly as a trial steering committee member; personal fees from Novo Nordisk as a trial steering committee member and consultant; consulting fees from Recor, Ardelyz, GlaxoSmithKline, Akebia, Endologix, Fibrogen, Provention, Becton Dickson, and Medtronic outside the submitted work. Dr Khera reported receiving personal fees from Tolmar, AbbVie Inc, Halozyme, Marius, and Endo Pharmaceuticals outside the submitted work. No other disclosures were reported.

Funding/support

The trial was funded by a consortium of testosterone manufacturers led by AbbVie Inc with additional financial support provided by Endo Pharmaceuticals, Acerus Pharmaceuticals Corp, and Upsher-Smith Laboratories. Dr Bhasin was supported in part by grant 3P30AG031679 from the Boston Claude D. Pepper Older Americans Independence Center.

Role of the funder/sponsor

The prostate substudy design and analysis plan were crafted by the TRAVERSE Prostate Substudy Committee led by the Research Program in Men's Health at the Brigham and Women's Hospital, Boston, Massachusetts (eAppendixes 1 and 2 in Supplement 3). The funder reviewed and made suggestions to the prostate substudy design and statistical analysis plan and oversaw the conduct, data collection, and management of the trial. The data analysis and interpretation of the data were performed by the statisticians associated with the Prostate Substudy Committee (K.B., K.M.P., T.G.T.). The first author (S.B.) wrote the first manuscript draft and all co-authors reviewed and approved the manuscript. The decision to submit the manuscript for publication was made by the academic leadership of the TRAVERSE Prostate Substudy Committee. The funder reviewed the manuscript, made suggestions on the content, and approved the final version of the manuscript.

Additional contributions

The members of the Prostate Adjudication Committee are as follows: Michael O'Leary, MD (chair), Scott Lucia, MD, Mark A. Preston, MD; A. John Kellog Parsons, MD, MHS. The members of the Data Monitoring Committee are as follows: John H. Alexander, MD, MHSc (chair), Duke Clinical Research Institute, Duke University, Durham, North Carolina; William Bremner, MD, PhD, University of Washington, Seattle; Eric Klein, MD, Cleveland Clinic, Cleveland, Ohio; Darren K. McGuire, MD, MHSc, University of Texas Southwestern Medical Center, Dallas; Janet Wittes, PhD, Wittes LLC, Washington, DC; Renato D. Lopes, MD, PhD (observer, nonvoting), Duke Clinical Research Institute, Durham, North Carolina; Andrew Armstrong, MD, ScM (ad hoc consult), Duke University Medical Center, Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, North Carolina.

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Supplementary files available here.

Please note: Only Testosterone 1% gel (ANDROGEL®) is currently registered by SAHPRA.

Please find the link to the newly open access to the main TRAVERSE publication, Cardiovascular Safety of Testosterone-Replacement Therapy https://www.nejm.org/doi/full/10.1056/NEJMoa2215025

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More info

SGLT2 inhibitors in type 2 diabetes mellitus: a pharmacist's guide to optimised care

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Abstract

Objectives: To review current evidence on sodium–glucose co-transporter-2 (SGLT2) inhibitors in the management of type 2 diabetes mellitus (T2DM), highlighting their mechanisms, efficacy, safety, and relevance to the growing burden of diabetes mellitus within the South African healthcare context, where high rates of undiagnosed disease and limited specialist access amplify the importance of pharmacist-led interventions. This review underscores the vital role of pharmacists as frontline diabetes care providers – facilitating optimal use of SGLT2 inhibitors such as empagliflozin and dapagliflozin through patient counselling, safety monitoring, and therapeutic guidance.

Methods: A narrative literature review was conducted by searching PubMed, Google Scholar, and local databases. Key articles on SGLT2 inhibitors, their effects on cardiovascular and renal outcomes, and prevalence data on T2DM in South Africa were included. Relevant clinical trials and meta-analyses published in English were appraised, with a focus on recent developments and guidelines.

Results: *Burden of diabetes in South Africa:* T2DM prevalence can reach 12.9% or higher in certain urban black populations, exceeding the overall International Diabetes Federation (IDF) estimate of 10.8%. Nearly half (45.4%) of those affected remain undiagnosed.
Mechanism and benefits: SGLT2 inhibitors lower blood glucose by enhancing urinary excretion of glucose, providing insulin-independent glycaemic control. They induce weight loss and mild blood pressure reductions.
Cardiorenal protection: Large-scale trials conducted in T2DM patients with either established chronic kidney disease or cardiovascular disease or high cardiovascular risk demonstrate meaningful reductions in cardiovascular events, hospitalisation for heart failure, and progression of chronic kidney disease.
Safety profile: While generally well tolerated, key adverse effects include genitourinary infections and rare euglycaemic ketoacidosis, especially during acute illness or low-carbohydrate intake.

Conclusion: SGLT2 inhibitors address both the escalating rates of T2DM in South Africa and its serious complications. Their robust cardiorenal benefits, combined with modest weight loss and minimal hypoglycaemia risk, make them an essential component of contemporary diabetes pharmacotherapy. Pharmacists play a central role in identifying appropriate candidates, advising on safety precautions, and improving patient outcomes in an increasingly burdened healthcare landscape.

Keywords: Sodium-glucose co-transporter-2 (SGLT2) inhibitors, canagliflozin, dapagliflozin, empagliflozin, efficacy, safety

https://doi.org/10.36303/SAPJ.2676

Introduction

Diabetes Mellitus (DM) is a significant and escalating health concern, both globally and in South Africa, driven by urbanisation and lifestyle changes.[1] Recent estimates place the local prevalence as high as 12.9% in some urban black populations – surpassing the country's overall IDF rate of 10.8% – with nearly half (45.4%) of all individuals remaining undiagnosed.[2,3]

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a revolutionary class of medications for the management of type 2 diabetes mellitus (T2DM). Beyond their primary glycaemic-lowering effects, SGLT2 inhibitors confer substantial cardiovascular and renal benefits, positioning them as essential medicines in diabetes care. The versatility of these agents is demonstrated by their FDA-approved indications, which include: enhancing glycaemic control in type 2 diabetes mellitus (T2DM) when used alongside diet and exercise; lowering the risk of major adverse cardiovascular events (such as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) in individuals with T2DM and established cardiovascular disease; reducing the likelihood of cardiovascular-related hospitalisation and mortality in patients with heart failure with reduced ejection fraction (NYHA class II-IV); slowing the progression of chronic kidney disease (CKD) by mitigating eGFR decline and reducing hospitalisation risk in at-risk patients; and improving cardiovascular outcomes in individuals with heart failure with preserved ejection fraction. Notably, dapagliflozin has received FDA approval for the treatment of heart failure across the entire spectrum of left-ventricular ejection fraction (LVEF).

This review provides pharmacists with a comprehensive overview of SGLT2 inhibitors in T2DM, focusing on their mechanisms, differences, side effect profiles, interactions, metabolism, safety considerations, and indications in special populations.

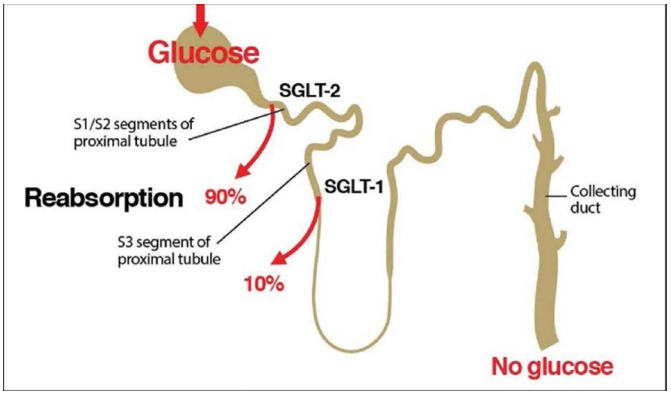

Figure 1: Mechanism of action of SGLT2 inhibitors

Adapted from[4]

Mechanism of action

Kidney glucose regulation

In individuals with normal health, most of the glucose (90%) that passes through the kidneys' filtration systems is reabsorbed by SGLT2 within the initial and middle sections of the proximal tubule (S1 and S2). The small amount of glucose that remains (10%) is then taken up by SGLT1 in the final portion (S3) of the same tubule (Figure 1).[4] Inhibiting SGLT2-mediated glucose reabsorption in the proximal tubule, thus enhances urinary glucose excretion and therefore reduces plasma glucose concentrations. This insulin-independent mechanism contributes to glucose control while also inducing osmotic diuresis, which leads to weight loss and a reduction in blood pressure. The unique insulin-independent nature of SGLT2 inhibitors results in a minimal risk of hypoglycaemia when used as monotherapy.[5-7]

Pharmacokinetics, metabolism and interactions

SGLT2 inhibitors, which are taken orally with a bioavailability in excess of 60%, exhibit variable protein binding and are primarily metabolised by hepatic glucuronidation via uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes, with renal and faecal excretion of metabolites (Table I).[5]

It is important to note that drugs influencing UGT enzyme activity may alter the metabolism of SGLT2 inhibitors. For example, inducers like rifampicin may decrease the plasma concentration of SGLT2 inhibitors, potentially reducing their efficacy (Table II).[8]

Pharmacists need to be vigilant particularly for patients with impaired hepatic or kidney function or those taking multiple medications such as concomitant use of UGT inducers (e.g. rifampicin, phenytoin, phenobarbital) as they can potentially reduce SGLT2 effectiveness, and inhibitors (e.g. kinase inhibitors, deferasirox, quercetin) which may cause elevated plasma levels and toxicity. Thus, potential interactions with UGT inducers/inhibitors should be monitored to mitigate these potential issues.

Interactions with other drugs and food

Because SGLT2 inhibitors are widely used for managing T2DM, they are often used in combination with other medications due

Table I: Comparative overview of SGLT2 inhibitors

Feature	Empagliflozin	Dapagliflozin	Canagliflozin (Canagliflozin (not registered in SA)
Selectivity for SGLT2	High	Moderate	Moderate
Half-life	12.4 h	12.2 h	11h–13 h
Dosing	10–25 mg OD	5–10 mg OD	100–300 mg OD
Oral bioavailability	> 60 %	78%	~ 65%
Plasma protein binding	86%	91%	98%
Hepatic metabolism	Extensive	Extensive	Extensive
Urinary elimination	28.6%	< 2%	< 1%
Cardiovascular benefits	Strongest evidence	Moderate evidence	Moderate evidence
Renal benefits	Yes (renal protection in chronic kidney disease [CKD])	Yes	Yes
Risk of genital infections	Moderate	Moderate	Higher
Bone fracture risk	No significant risk	No significant risk	Increased risk
Administration (with/without food)	With or without food	With or without food	Preferably before first meal.[4,5]
Trade name (numerous generics available in SA)	Jardiance 10 mg, Jardiance 25 mg (SA, US, EU)	Forxiga 5, Forxiga 10 (SA, US, EU)	Invokana 100, Invokana 300 (US, EU)

Abbreviations: US, United States of America; EU, Europe; SA, South Africa

Table II: Metabolism and UGT enzyme interactions of SGLT2 inhibitors[8]

SGLT2 inhibitor	Primary UGT enzymes involved	Effect of UGT inducers (e.g. rifampicin)	Clinical implication
Dapagliflozin	UGT1A9	↓ Plasma concentration	May reduce efficacy – monitor glycaemic control
Canagliflozin	UGT1A9, UGT2B4	↓ Plasma concentration	Dose adjustment may be necessary
Empagliflozin	UGT1A3, UGT1A8, UGT1A9, UGT2B7	↓ Plasma concentration	Monitor response; limited data on dose adjustment necessity

Table III: Drug and food interactions of SGLT2 inhibitors

Interaction	Potential effect
Diuretics	Enhanced diuresis and increased risk of dehydration and hypotension, especially in elderly patients.[9]
Insulin and sulfonylureas	The risk of SGLT2 inhibitors as monotherapy is low, however, increased risk of hypoglycaemia when used together, as both drugs lower blood glucose.[9,10]
NSAIDs (e.g. mefenamic acid)	Potential for reduced renal function, especially in elderly or volume-depleted patients. Mefenamic acid inhibits UGT1A9, increasing dapagliflozin plasma exposure.[8]
Probenecid	Increases plasma exposure of canagliflozin due to UGT enzyme inhibition, but the interaction is not clinically significant.[8]
Rifampicin	Reduces plasma levels of dapagliflozin and canagliflozin due to UGT enzyme induction, which may reduce effectiveness. Canagliflozin dose adjustment may be required.[9]
Other UGT inducers (phenytoin, phenobarbital, ritonavir)	Can reduce plasma levels of canagliflozin, requiring dose adjustment to 300 mg if tolerated.[8]
Paracetamol	No clinically relevant interaction observed.[8]
Warfarin	No significant effect on warfarin pharmacokinetics, no dose adjustment required.8
Digoxin	Canagliflozin may slightly increase digoxin levels, requiring monitoring of plasma digoxin concentrations.[9]
Simvastatin	Slight increase in simvastatin levels, but not clinically significant.[9]
Valsartan	Minor increase in valsartan exposure, but no clinical significance.[9]
Oral contraceptives	Canagliflozin may slightly increase ethinyl oestradiol and levonorgestrel exposure, though the effect is not significant.[9]
Thiazide diuretics	No significant pharmacokinetic interactions with hydrochlorothiazide.[9]
Food	SGLT2 inhibitors can be taken with or without food. However, canagliflozin is recommended to be taken before the first meal of the day for optimal absorption.[9]

to numerous comorbidities of lifestyle diseases. While SGLT2 inhibitors may interact with drugs that inhibit or induce UGT enzymes, their additional effects on renal glucose excretion and osmotic diuresis necessitate caution when used with diuretics, antihypertensives, and insulinotropic agents to prevent adverse outcomes such as dehydration, hypotension, or hypoglycaemia.[8,9] Table III outlines key drug and food interactions associated with SGLT2 inhibitors.

Clinical efficacy of SGLT2 inhibitors

SGLT2 inhibitors reduce HbA1c levels by approximately 0.6%–1.0%.[11,12]

A systematic review and meta-analysis evaluated SGLT2 inhibitors in 45 placebo-controlled studies involving 11 232 participants, and 13 studies with active comparators including 5 175 participants.[13] This systematic review indicated that SGLT2 inhibitors, when compared with other antidiabetic agents, promote weight reduction and lower systolic blood pressure. Specifically, a meta-analysis demonstrated that SGLT2 inhibitors are associated with a mean weight loss of 1.8 kg (95% CI: 0.11–3.50 kg). Additionally, they contribute to a reduction in systolic blood pressure by an average of 4.45 mmHg (95% CI: 3.18–5.73 mmHg).

Beyond glycaemic control, recent data have shown that SGLT2 inhibitors provide significant cardiovascular and renal benefits.

Cardiovascular and renal protection

Cardiovascular disease is the foremost contributor to mortality in South Africa, second only to HIV/AIDS.[14]

Large-scale clinical trials have demonstrated SGLT2 inhibitors' ability to reduce major adverse cardiovascular events (MACE), lower cardiovascular mortality, and decrease hospitalisation for heart failure (HF) (Table IV). The EMPA-REG trial highlighted a 38% reduction in cardiovascular mortality with empagliflozin in patients with T2DM and high cardiovascular risk.[15] These findings were further supported by DAPA-HF and DECLARE-TIMI 58, which confirmed the benefit of dapagliflozin in reducing heart failure-related hospitalisations.[16,17]

Exact nationwide incidence data on CKD in South Africa are limited, but are estimated at more than 10% of adults, primarily due to poorly controlled hypertension and T2DM. Local renal registry reports show a rising number of patients progressing to end-stage kidney disease (ESRD), with both hypertension and T2DM frequently implicated.[18]

In addition to cardiovascular protection, SGLT2 inhibitors have been shown to preserve renal function and slow the progression of chronic kidney disease (CKD). The CREDENCE[19] and DAPA-CKD[20] trials demonstrated a significant reduction in CKD progression, even in patients without diabetes. These findings have led to their widespread recommendation in guidelines for patients with established cardiovascular disease (CVD), heart failure with reduced ejection fraction (HFrEF), and CKD, regardless of diabetes status.[21] As a result, SGLT2 inhibitors are now a cornerstone therapy for improving outcomes in these high-risk populations and current guidelines (consensus report of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and European Society of Cardiology (ESC) recommend the inclusion of SGLT2 inhibitors in the management of these conditions to improve patient outcomes.[22]

Table IV: Cardiovascular and renal protection data

Study	Drug	Population	Primary outcome	Key findings
EMPA-REG OUTCOME[15]	Empagliflozin	T2DM patients with high CV risk	Cardiovascular mortality	**38% reduction in CV death.** ↓ MACE, 0.86 (0.74–0.99) ↓ HHF ($p = 0.04$)
DAPA-HF[16]	Dapagliflozin	Patients with HFrEF (with/without T2DM)	Heart failure outcomes	**26% reduction in hospitalisation for heart failure.** At ($p < 0.001$) ↓ reduction of CV death and HF 0.74 (0.65–0.85)
CREDENCE[19]	Canagliflozin	T2DM patients with CKD	CKD progression	**30% reduction in CKD progression.** ↓ ESRD, doubling of sCr, renal death, or CV death at ($p = 0.00001$) 0.70 (0.59–0.82)
DAPA-CKD[20]	Dapagliflozin	CKD patients (with/ without T2DM)	CKD progression, mortality	**39% reduction in CKD progression, 31% reduction in all-cause mortality.** At ($p < 0.001$) ↓ Decline in eGFR, new ESRD, CV death or renal death, 0.61 (0.51–0.72)
DECLARE-TIMI 58[17]	Dapagliflozin	T2DM patients with or at risk for CV disease	Cardiovascular safety	**27% reduction in hospitalisation for heart failure.** At ($p = 0.005$) ↓ CV death or HHF 0.83 (0.73–0.95)

Abbreviations: CV, Cardiovascular; MACE, Major Adverse Cardiovascular Events; HHF, Hospitalisation for Heart Failure; HFrEF, Heart Failure with reduced Ejection Fraction; T2DM, Type 2 Diabetes Mellitus; CKD, Chronic Kidney Disease; ESRD, End Stage Renal Disease; sCR, serum Creatinine.

These findings underscore the multifaceted benefits of SGLT2 inhibitors, extending beyond glucose lowering to include significant cardiovascular and renal protection.[6]

Safety considerations

Potential adverse effects linked to SGLT2 inhibitors encompass urinary tract infections, genital fungal infections, Fournier gangrene, hypovolaemia and low blood pressure, acute kidney injury, diabetic ketoacidosis, as well as a heightened likelihood of osteoporosis and fractures (Table I).[23]

Genitourinary infections

Although SGLT2 inhibitors are generally well tolerated, they are associated with some important safety concerns. One of the most common adverse effects is an increased risk of genitourinary infections, including fungal infections and urinary tract infections, due to elevated glucose levels in the urine.[24]

Ketoacidosis

A rare but serious complication is euglycaemic ketoacidosis, which can occur even with normal blood glucose levels, particularly in cases of dehydration, reduced carbohydrate intake, or acute illness. During these states, the body may increase ketone production despite normal glucose levels, leading to ketoacidosis. It is thus essential for healthcare providers to be aware of this potential adverse effect to ensure prompt recognition and appropriate management.[25]

Hypotension

Furthermore, the osmotic diuresis induced by SGLT2 inhibitors may result in hypovolaemia and hypotension, necessitating caution in patients taking diuretics or those with a low baseline blood pressure.[26]

Fractures and lower limb amputations

Another significant concern is the potential for fractures and lower limb amputations, particularly with canagliflozin, which has been linked to an increased risk of these events.[27] As a result, careful patient selection and monitoring are necessary, especially for individuals at high risk for falls, fractures, or peripheral vascular disease.

Special populations

Renal impairment

Chronic kidney disease (CKD) is anticipated to rank as the fifth leading cause of death worldwide by 2040, with diabetic kidney disease (DKD) being the primary driver of this alarming trend.[28] Encouragingly, recent evidence has shown that SGLT2 inhibitors offer substantial renal and cardiovascular protection.[19,20] As a result, current clinical guidelines now recommend these therapies for individuals living with both CKD and DM to slow disease progression and improve outcomes.[22]

The efficacy of SGLT2 inhibitors diminishes as renal function declines, necessitating careful consideration in patients with renal impairment. Specifically, their glucose-lowering effect is reduced in individuals with an estimated glomerular filtration rate (eGFR) below 45 mL/min/1.73 m^2, and they are generally not recommended for use when eGFR falls below this threshold (Table V).[29]

However, certain SGLT2 inhibitors have demonstrated renal protective benefits even in patients with eGFR as low as 30 mL/min/1.73 m^2, suggesting potential use in this population under specialist guidance.[30-32]

Over time, a variety of clinical trials evaluating different SGLT2 inhibitors across diverse patient groups and focusing on varied primary and secondary outcomes – including several post hoc analyses – have deepened our understanding of how these agents

Table V: SGLT2 inhibitors dose adjustment in renal and hepatic impairment

	CKD Stage 3b (eGFR 30–44 mL/min/1,73 m²)	CKD Stage 4 (eGFR 15–29 mL/min/1,73 m²)	CKD Stage 5 (eGFR < 15 mL/min/1,73 m²)	Hepatic dysfunction
Canagliflozin	100 mg	Do not initiate if eGFR < 45.[29]		Avoid in severe impairment (Child-Pugh class C)[30]
Dapagliflozin	10 mg	Do not initiate if eGFR < 25. If previously taking, may continue until dialysis.[29] Initiation is not recommended if eGFR < 25; however, patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death, and heart failure.[23]		No dosage adjustment; use with caution if initiating in severe impairment[30]
Empagliflozin[33]	10 mg, 25 mg	No dosage adjustment necessary for eGFR ≥ 30 (SA PI), eGFR ≥ 20.[29,34] Empagliflozin is not advised in patients with an eGFR < 30 and is contraindicated in those receiving dialysis**.** Due to limited evidence, no dosing guidance is available for individuals with T2DM and cardiovascular disease if eGFR is < 30, or for those with heart failure with reduced ejection fraction and eGFR < 20.[23]		No dosage adjustment necessary[29]

Adapted from[23,30]

may help prevent and manage CKD.[19,20] To fully grasp the impact of SGLT2 inhibitors on renal protection**,** it is essential to consider the combined findings from the CREDENCE[19] and DAPA-CKD[20] studies, which together paint a more comprehensive picture of their therapeutic value in CKD care.[32]

Hepatic impairment

In hepatic impairment, while specific dose adjustments may not be universally required, caution is advised, particularly in severe cases, due to limited data on safety and efficacy (Table V).

Pregnancy and lactation

The use of SGLT2 inhibitors during pregnancy and lactation is not recommended due to potential risks to foetal and neonatal development.[34] Human data are limited, but the few that are available suggest an increased incidence of miscarriages and congenital anomalies associated with SGLT2 inhibitor use during pregnancy.[34] Furthermore, these agents are excreted in animal milk, and their effects on the breastfed infant are unknown; therefore, breastfeeding is not advised during SGLT2 inhibitor therapy.[34] Healthcare providers should counsel women of childbearing potential on these risks and consider alternative glucose-lowering therapies during pregnancy and lactation.[34]

Take home messages for pharmacists

Pharmacists should be aware that SGLT2 inhibitors induce osmotic diuresis, which can lead to increased urination, volume depletion, and hypotension.[35] It is important to counsel patients to maintain adequate hydration (preferably water) and electrolyte balance to prevent dehydration and dizziness.[36]

Similarly, caution is advised if the patient is on diuretics, as concomitant loop or thiazide diuretics can exacerbate fluid loss – dose adjustments may be needed to avoid hypotension.[37]

Educate patients about the rare risk of euglycaemic diabetic ketoacidosis (DKA): this can occur even with normal blood glucose, so advise them to be vigilant for warning signs (e.g. nausea, vomiting, abdominal pain, or a fruity breath odour) and seek immediate medical attention if these occur.[38,39]

In addition, pharmacists should advise withholding the SGLT2 inhibitor during any acute serious illness (such as vomiting, severe infection, or dehydration) or prior to major surgery, and restarting only once the patient's condition stabilises.[36] This "sick day" precaution helps reduce the risk of DKA in stressful conditions.

Pharmacists also play a key role in preventing and managing infections associated with SGLT2 inhibitors. Because these drugs cause persistent glucosuria, they increase the risk of genital fungal infections (e.g. candidal vulvovaginitis or balanitis).[39] Emphasise good perineal hygiene – keeping the genital area clean, dry, and following proper daily washing – to reduce this risk. Patients should be counselled to report any signs of genital infection or urinary tract infection promptly so that treatment can be initiated.

Another important point is managing drug interactions: SGLT2 inhibitors alone have a low hypoglycaemia risk, but when combined with insulin or sulfonylureas, there is an increased risk of hypoglycaemia.[35] Therefore, the doses of insulin or secretagogues may need to be reduced to prevent hypoglycaemic episodes.

Similarly, blood pressure and volume status should be monitored if patients are on antihypertensives or diuretics, given the additive hypotensive effect.[15]

Renal function monitoring is advisable as well – check baseline and periodic kidney function – since these agents rely on glomerular filtration to exert their effect. Efficacy diminishes in advanced kidney disease, and most SGLT2 inhibitors are not recommended for glycaemic control in patients with significantly reduced eGFR (generally < 45 mL/min/1.73 m²). Refer to Table V.[29]

By staying vigilant about hydration status, infection prevention, potential interactions, and appropriate monitoring, pharmacists can ensure safe dispensing of SGLT2 inhibitors and provide valuable counselling to optimise patient outcomes.

Pharmacist Quick Tips

- Counsel on DKA symptoms and hydration
- Withhold during acute illness/surgery
- Monitor renal function regularly

- Adjust insulin/sulfonylurea doses to prevent hypoglycaemia
- Watch for genital infections – advise on hygiene
- Be alert to UGT-related drug interactions

Conclusion

SGLT2 inhibitors have revolutionised the management of T2DM by offering glycaemic control alongside significant cardiovascular and renal benefits. Their role in reducing heart failure hospitalisations and slowing CKD progression makes them a valuable addition to diabetes care. However, optimising their use requires pharmacist-led interventions, including patient education, monitoring for adverse effects, and ensuring appropriate therapy selection. By integrating SGLT2 inhibitors effectively into individualised treatment plans, pharmacists can enhance patient outcomes and contribute to a holistic approach to diabetes management.

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Advances in hypothyroidism management: rethinking therapy beyond levothyroxine

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Abstract

Hypothyroidism, a prevalent neuroendocrine disorder characterised by insufficient thyroid hormone production and a wide spectrum of clinical manifestations, affects approximately 5% of the population, with an additional 5% remaining undiagnosed. While levothyroxine remains the golden standard of care, its inability to resolve persistent symptoms in a subset of patients highlights the need for alternative approaches. Combination levothyroxine+liothyronine therapy, though unpopular and underutilised by most physicians, offers potential benefits, particularly when tailored to mimic natural thyroid hormone ratios. Furthermore, emerging therapies show promise in reducing pharmacokinetic fluctuations that limit current advances in hypothyroidism therapy. By addressing the shortcomings of traditional therapies, these innovative approaches aim to improve the quality of life and clinical outcomes for patients with hypothyroidism, especially when the golden standard fails. This review highlights current viable options and explores emerging therapeutic strategies that could potentially optimise current treatment and quality of life, catering for all hypothyroidism patients.

Keywords: hypothyroidism, levothyroxine, liothyronine, novel thyroid hormone formulations, T4/T3 combination therapy

https://doi.org/10.36303/SAPJ.3267

Introduction

Hypothyroidism is the most common hormone deficiency disorder[1] affecting approximately 5% of the general population, with an additional 5% estimated to be undiagnosed.[2] Despite its global prevalence, epidemiological data highlighting the prevalence of hypothyroidism in South Africa is currently very limited. However, it is well established that women are five to ten times more likely to develop hypothyroidism than men, with the likelihood increasing with age, during pregnancy, postpartum, and menopause.[3] Hypothyroidism occurs when there is insufficient production of thyroid hormone to meet the body's requirements,[2] which can result in a range of subtle to life-threatening symptoms, if not adequately treated and monitored.[2] The thyroid gland, located in the neck, is responsible for the production of the prohormone thyroxine/tetraiodothyronine (T4) and its activation to form its biologically active counterpart, triiodothyronine (T3) (Figure 1).[2-3] Both T3 and T4 are collectively termed thyroid hormone.[2] Conversion of T4 to T3 occurs through a process called deiodination by 5′ deiodinase enzymes, which remove an iodine atom from T4.[4] Deiodinase is also responsible for producing metabolically inactive T3 known as reverse T3.[4]

Hypothyroidism pathophysiology

Secretion and production of thyroid hormone are under the control of a self-regulatory circuit known as the hypothalamic-pituitary-thyroid (HPT) axis (Figure 2).[6] This neuroendocrine system regulates the production and secretion of thyroid hormone.[6] In this system, the thyroid releasing hormone (TRH) is produced by the neurons of the hypothalamus known as the paraventricular nuclei.[7] This stimulates the secretion of thyroid stimulating hormone (TSH), also known as thyrotropin, by the pituitary gland, which binds to its membrane receptor on the thyroid, facilitating the release of T4 and T3.[7] Iodine is the main micronutrient required

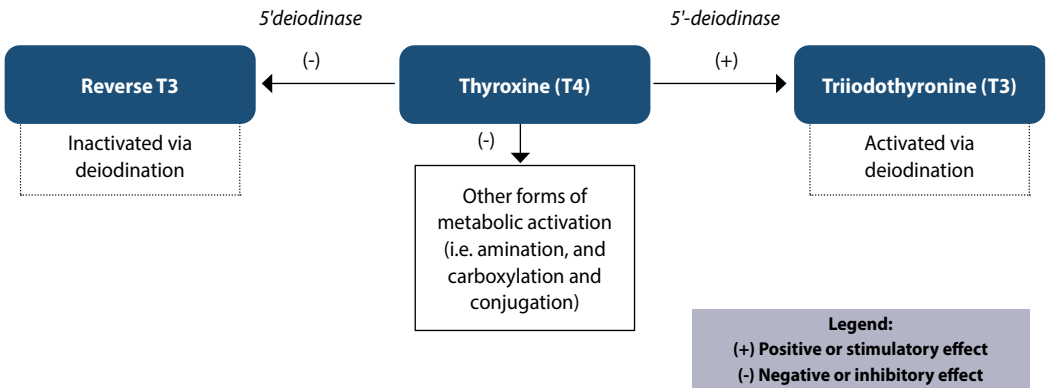

Figure 1: The metabolic pathways of thyroxine (T4)[5]

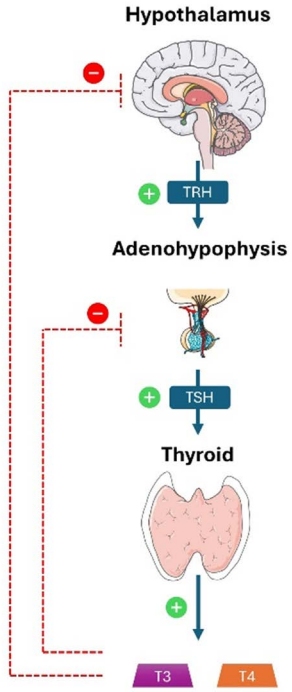

Figure 2: A visual representation of the hypothalamus-pituitary-thyroid (HPT) axis.[7] Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus and stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH), which in turn stimulates the thyroid gland to produce and release triiodothyronine (T3) and thyroxine (T4).

for this process, serving as a component of T4 and T3.[8] When there is a high concentration of thyroid hormone (T4 + T3) in the blood, a negative feedback mechanism is activated to inhibit the further secretion of the hormone by the pituitary gland, ensuring that homeostasis is maintained.[6-7] A disruption in the function of any of the three components of the HPT axis (hypothalamus, pituitary gland or thyroid gland) can lead to insufficient production of thyroid hormone and thus hypothyroidism.[9] Depending on the origin of the disruption, hypothyroidism can be classified into various types.

Classifications of hypothyroidism and their causes

Hypothyroidism can be classified into primary, secondary, and tertiary types.[10] While over 99% of hypothyroidism cases are due to failure of the thyroid gland (primary), causes of hypothyroidism may alternatively be due to insufficient TSH from the pituitary gland (secondary) or insufficient TRH from the hypothalamus (tertiary).[2] Secondary and tertiary hypothyroidism are rare and often present with the same clinical manifestations,[10] consequently, they are collectively termed central hypothyroidism.[2,10]

Primary hypothyroidism

Primary hypothyroidism is mainly caused by iodine irregularities or autoimmune thyroiditis, commonly referred to as Hashimoto's disease. In addition to this, there are many other causes which are highlighted in Table I.[11-12] Both excess iodine and the deficiency thereof can induce hypothyroidism.[13] Excess iodine can result from external radiation, radioactive iodine, and certain medications, such as amiodarone and lithium, which can affect thyroid function and subsequently hormone production.[3] Additionally, medications like β-blockers and corticosteroids inhibit 5'-deiodinase activity, critical for the conversion of T4 to T3, further impairing thyroid hormone synthesis. Both excess iodine and the deficiency thereof can induce hypothyroidism.[13] Excess iodine can result from external radiation, radioactive iodine, and certain medications, such as amiodarone and lithium, which can affect thyroid function and subsequently hormone production.[3] Additionally, medications like β-blockers and corticosteroids inhibit 5'-deiodinase activity, critical for the conversion of T4 to T3, further impairing thyroid hormone synthesis.[14]

Nevertheless, environmental iodine deficiency is the most common cause of hypothyroidism.[2] Reduced iodine content in

Table I: Causes of hypothyroidism[12-13]

Primary Hypothyroidism	Central Hypothyroidism
Loss of functional thyroid tissue	Pituitary or hypothalamic neoplasms
Hashimoto's thyroiditis	Trauma (surgery, head injury)
Surgical removal of the thyroid	Radiation ischaemic necrosis (postpartum pituitary infarction/ Sheehan's syndrome, severe shock, diabetes mellitus)
Radioiodine ablation, external irradiation of the thyroid	Vascular (haemorrhage, aneurysm of the internal carotid artery)
Silent and postpartum thyroiditis	Infections (abscess, tuberculosis, syphilis, toxoplasmosis)
Cytokine-induced thyroiditis	Infiltrative disorders (sarcoidosis, histiocytosis, haemochromatosis)
Invasive fibrous thyroiditis	Lymphocytic hypophysitis
Thyroid infiltration (amyloidosis, haemochromatosis, sarcoidosis, scleroderma, cystinosis, primary thyroid lymphoma)	Drugs (bexarotene)
Thyroid dysgenesis	Set point diseases (infants born to mothers with poorly controlled Graves' disease)
Functional defects in thyroid hormone biosynthesis and release	Genetic mutations
Iodine deficiency and iodine excess	Idiopathic
Thyroid hormone biosynthetic defect	
Drugs: antithyroid agents, lithium, amiodarone, tyrosine kinase inhibitors (e.g. sunitinib), ethionamide, sulphonamides, goitrogenic chemicals, thalidomide	
Peripheral (extrathyroidal) hypothyroidism	
Large haemangioma	
Thyroid hormone resistance	

soil across many regions results in crops with insufficient iodine levels, leading to dietary intake below the daily requirement for synthesising thyroid hormones, particularly T4.[15] To address this, many countries, including South Africa, have implemented iodine fortification programmes, such as iodising salt and common food items, to reduce the prevalence of iodine-deficiency-induced hypothyroidism.[13] In areas with sufficient iodine, Hashimoto's disease is the most common cause of hypothyroidism.[2] This disease occurs due to an immune-mediated destruction of the thyroid gland by cytotoxic T-lymphocytes and autoantibodies.[6] As a result, fibrosis may reduce thyroid gland size and lead to hypothyroidism.[6] While the precise mechanisms underlying Hashimoto's disease remain unclear, it is believed that genetic and environmental factors play a causative role.[13]

Central hypothyroidism

Central hypothyroidism is caused by impaired production of TSH from the pituitary gland, leading to inadequate stimulation of an otherwise normal thyroid gland to produce thyroid hormone.[1,16] Since the pituitary is stimulated by TRH, which is released by the hypothalamus, hypothyroid impairments are frequently linked to the hypothalamus as well.[13] As a result, secondary hypothyroidism, which arises from the pituitary gland, and tertiary hypothyroidism, which originates in the hypothalamus, are collectively referred to as central hypothyroidism.[13,16] Secondary and tertiary hypothyroidism are uncommon, occurring in less than 1% of hypothyroidism cases.[1] Contrary to primary hypothyroidism, central hypothyroidism has a uniform prevalence in both sexes.[1,13] The causes of central hypothyroidism are listed in Table I[13] and include pituitary adenomas, head trauma, radiation, various surgical procedures and genetics.[13]

Signs and symptoms of hypothyroidism

The thyroid hormone impacts nearly every organ system in the body, including the heart, nervous system, bones, and gastrointestinal tract.[6] This is because thyroid hormone plays diverse roles in the regulation of metabolism, growth, neural differentiation and normal development of mammals, resulting in a range of symptoms when production is disturbed.[17] Table II provides a broad overview of the effects of thyroid hormone, emphasising its diverse roles and impact on bodily functions.[6] Thyroid hormone production is particularly vital during pregnancy, as it supports foetal development, placing an increased demand on the mother's thyroid gland to meet the needs of both mother and foetus.[18] In infants, conditions of hypothyroidism during development manifest as significant neurological deficits and growth retardation.[17] In contrast, symptoms in adults range from subtle[17] to life-threatening, with subtle symptoms including fatigue, depression, weight gain, voice changes, dry skin, lethargy, constipation, sleep disorders, muscle cramps, oedema, and cold intolerance, while the most serious symptom is myxoedema coma.[19] Hypothyroidism typically presents with numerous symptoms that are normal to ageing and easily attributable to other disorders, making clinical manifestations an unreliable method for diagnosis.[3]

Diagnosis

Diagnosis of hypothyroidism may begin with a physical examination for course skin, delayed ankle reflex, and other common symptoms.[3] However, due to low specificity of these signs, a clinical evaluation should be accompanied with a diagnostic work up.[3] Blood tests to assess TSH and free T4 levels are essential for confirming the diagnosis.[19] Primary hypothyroidism is characterised by reduced free T4 and elevated TSH levels, while central hypothyroidism may present with normal/low TSH levels and low free T4 levels.[19] Additional testing that reveals elevated thyroid peroxidase antibodies supports the diagnosis of autoimmune hypothyroidism.[19]

Blood test levels of T4 and TSH are further classified into two diagnostic categories that guide treatment: subclinical hypothyroidism and overt hypothyroidism.[12] Subclinical hypothyroidism is a mild form of hypothyroidism, biochemically diagnosed when there are elevated TSH concentrations while free T4 and T3 serum concentrations remain within the normal range.[12] This grade of hypothyroidism is usually an indicator that the thyroid is starting to underperform, but is still maintaining normal thyroid hormone production.[12] Patients are usually treated when TSH levels rise above 10 mIU/L, as this threshold suggests a greater risk of progression or complications.[12] In pregnant women, however, most clinicians treat subclinical hypothyrodism

Table II: Organ and system involvement of thyroid hormone and its resulting effects[6,18]

Organ/system	Effect	Result
Heart	Increased β-receptor expression	Increased heart rate, stroke volume, cardiac output and contractility
Lungs	Stimulate respiratory centres	Increased perfusion and oxygenation
Skeletal muscle	Increased development of Type II (fast twitch) muscle fibres.	Increased capability for fast and powerful contractions
Metabolism	Increased Na+/K+ ATPase expression and basal metabolic rate	Increased oxygen consumption, respiration rate and body temperature
Growth during childhood	Induction of chondrocytes, osteoblasts and osteoclasts. Assist axonal growth and myelin sheath formation	Bone growth Brain maturation
Hypothalamic-pituitary gonadal axis	Regulates kisspeptin and gonadotropin-releasing hormone directly, and indirectly through prolactin and leptin. Affects the biological availability of sex steroids	Development and maintenance of the ovary, uterus and endometrium Regulates placental and foetal development during pregnancy

even when TSH levels are below 10 mIU/L due to the risks that low thyroid hormone levels pose to foetal development.[12] In some cases, subclinical hypothyroidism can progress to overt hypothyroidism,[12] a more intense form of hypothyroidism characterised by elevated TSH accompanied by low serum free T4 concentrations.[20] Overt hypothyroidism is particularly common in women who are of reproductive age and warrants treatment regardless of symptom severity.[20] This grade of hypothyroidism is mostly permanent and requires lifelong management and treatment.[12]

Treatment

Levothyroxine

Replacement therapy with levothyroxine (LT4) monotherapy currently serves as the standard of care for hypothyroidism.[21] Synthetically produced T4, LT4, is identical to the hormone secreted by the thyroid gland and can be converted to T3 when appropriately regulated by peripheral tissues (Figure 1). This results in the maintenance of a steady secretion of thyroid hormone to meet the body's requirements.[12] An advantage of LT4 therapy is its long half-life of seven days, allowing single daily doses and maintenance of patient safety in the case of omission or lack of compliance for a day.[12] The greatest challenge with LT4, however, lies in its low therapeutic index (TI) and the fact that normalising TSH levels does not always correspond with the normalisation of other markers of hypothyroidism.[21] Due to its narrow TI, precise dosing of LT4 is critical.[11] Typical dosages for women are 100–125 µg/day and 125–150 µg/day for men, with T4 requirements varying, depending on body weight and surface area, age, and pregnancy status.[11] Dosing in individuals with ischaemic heart disease or those over 60 should typically start with between a fourth and half of the expected dosage, while pregnant women require higher dosages due to increased hormone requirements.[3]

Side effects of levothyroxine therapy

Though LT4 is identical to thyroid-secreted T4, there are clinical consequences to excessive administration, and this is unfortunately common in clinical practice.[12] A notably high proportion (15–38%) of LT4 patients have been found to present with TSH levels dropping below reference range, indicative of over-replacement, thus highlighting the importance of close monitoring of TSH levels.[22] Furthermore, LT4 therapy presents with several adverse effects including reduction in bone density, especially in post-menopausal women,[12] increased risk of fracture, atrial fibrillation, stroke and bleeding.[11]

Limitations of current LT4 monotherapy

Standard hypothyroidism therapy has three main limitations.[23] Firstly, an estimated 10–20% of patients remain symptomatic despite the normalisation of TSH levels.[23] These patients experience the persistence of residual cognitive symptoms, difficulties managing body weight, and elevated cholesterol levels, all of which significantly reduce their quality of life and diminish the perceived benefits of treatment.[23]

Secondly, patients treated with LT4 may exhibit a relative and sometimes absolute deficiency of LT3.[24-25] This is because although LT4 effectively normalises pituitary TSH levels, it does not consistently restore T3 levels in peripheral tissues.[26-27] This discrepancy arises because T4 itself can inhibit the activity of Type 2 5′-deiodinase, thereby creating a localised T3 deficiency despite normal serum TSH levels.[26-27]

Lastly, the efficacy of LT4 therapy may also be influenced by genetic factors and comorbid conditions.[28] For instance, patients with polymorphisms such as Thr92Ala in the iodothyronine deiodinase 2 gene, which encodes Type 2 5′-deiodinase, often show improved outcomes with combination therapy compared to levothyroxine monotherapy.[29] These genetic variations reduce the catalytic activity of Type 2 5′-deiodinase, impairing the conversion of T4 to T3 in tissues (Figure 1).[29] Such genetic predispositions, combined with other comorbidities, help explain the persistence of symptoms in some patients, even when serum TSH levels are within the normal range.[12,30]

Combination LT4+LT3 therapy

In cases where persistent hypothyroidism symptoms occur despite normal TSH concentrations in patients treated with LT4, a combination of LT4 and LT3 therapy may be considered.[31] Currently, no combined formulation of T3 and T4 adequately mimics the relative concentrations of thyroid hormone produced naturally by the human thyroid.[12] Furthermore, no formulation allows the sustainable release of T4 and T3 as they would be released by the human thyroid.[12] As a result, and in many cases, combination therapy has been ruled out by many clinicians because there is no clear benefit when compared to LT4 monotherapy.[12]

Nevertheless, the limitations of LT4 therapy and the need for alternatives have driven the development of new therapeutic approaches, including transitioning patients to a combination of LT4 and LT3 in ratios designed to mimic the natural thyroid.[23] Clinical studies have tested multiple ratios, concluding that a range of 13:1 to 20:1 (T4:T3) effectively replicates the thyroid gland's output.[32-33] When administered at appropriate ratios, combination therapy is as effective as LT4 monotherapy in resolving hypothyroidism symptoms and normalising TSH levels.[23] Despite this evidence, many clinicians continue to view LT4 monotherapy as the gold standard, highlighting the need for greater awareness of combination therapy's potential benefits.[23]

While this approach has mainly been explored in other countries, it is readily applicable in South Africa as LT4 (commonly known as Levothyroxine)[34] and LT3 (commonly Liothyronine)[35] are available. Physicians can enhance treatment outcomes for patients on LT4 who continue to experience hypothyroidism symptoms by carefully titrating LT4 and LT3 doses to replicate physiological thyroid hormone release more closely.[32]

Liothyronine sodium monotherapy

Liothyronine is the synthetic form of T3 hormone produced by the body.[12] Unlike T4, it requires more than one daily dose due

to its short half-life of one day.[12] In addition to its short half-life, LT3 gives rise to extremely high serum T3 levels (between 250–600%) in its absorption phase, resulting in adverse effects, commonly cardiovascular effects such as palpitations.[12] These pharmacokinetic fluctuations and associated cardiovascular risks have led many clinicians to question the benefits of LT3 therapy.[12,23] Despite these concerns, evidence suggests that T3-containing therapies are as safe as LT4 therapy when serum TSH levels are maintained within the normal range.[23] This further highlights the efficacy of combination LT4+LT3 therapy.[23,36] Liothyronine monotherapy may also be considered in rare cases of LT4 malabsorption or in patients who struggle to metabolise LT4 to LT3.[12]

Novel approaches to current available hormone replacement therapy

New slow-release T3 formulations are under development to address the rapid absorption and metabolism of current LT3 formulations, which lead to rapid fluctuations in serum T3 levels.[23] While current evidence does not associate these fluctuations with adverse outcomes, especially when TSH levels are normalised, the goal remains to achieve stable serum T3 levels.[23] Current and emerging approaches for slow-release formulations include modified matrix systems made from components such as magnesium stearate, mannitol, or calcium phosphate, designed to slow LT3 release in the intestine.[37] Clinical trials with these capsules have shown slight reductions in intestinal LT3 release and lower serum peaks.[38] However, sustained serum T3 levels were not consistently observed,[39] highlighting challenges in identifying matrix combinations capable of reliably stabilising LT3.[38]

Another promising approach is T3-Sulphate (T3-S), which involves chemically modifying T3 by attaching a sulphate group.[40] This combination inactivates T3 while improving its water solubility.[40] The liver and certain gastrointestinal bacteria can reactivate T3-S by desulfation, slowly converting it back to active T3 and releasing it into circulation.[41] A recent phase II study in hypothyroid patients, where 25 µg of LT4 was replaced with 40 µg of T3-S, demonstrated significant reductions in mean T4 levels without fluctuations in T3 levels.[42] These results suggest that T3-S could help maintain stable T3 levels while preserving a physiological T4:T3 ratio.[42]

Lastly, a novel candidate molecule, poly-zinc-LT3, is a supramolecular complex with mucoadhesive properties and controlled hydrolysis behaviour.[40] Its muco-adhesion to the gastrointestinal tract, combined with gradual hydrolysis, enables sustained LT3 release and absorption.[43] A crossover randomised controlled trial in healthy volunteers showed a 30% reduction in C_{max} for poly-zinc-LT3, delayed by an hour, with an extended plateau lasting up to six hours.[44] At 24 hours, serum T3 remained above half of the C_{max}, demonstrating an improved pharmacokinetic profile.[44]

Conclusion

Millions of individuals worldwide are affected by hypothyroidism, a complex neuroendocrine disorder characterised by insufficient thyroid hormone production and, subsequently, a wide range of clinical manifestations. While LT4 monotherapy remains the standard treatment in most healthcare settings, limitations such as unresolved symptoms in some patients highlight the need for alternative approaches. Combination LT4+LT3 therapy, previously dismissed by many clinicians due to inconclusive evidence of its benefits, is now demonstrating renewed potential when tailored to mimic physiological thyroid hormone release. In South Africa, the availability of LT4 and LT3 provides a unique opportunity to explore combination therapy as a means to improve patient outcomes. Moreover, staying informed about global advancements in hypothyroidism management, including novel therapies, positions South Africa to integrate these innovations into clinical practice as they become accessible, ensuring improved care for patients in the future.

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Heart failure: understanding the condition and navigating its management

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Abstract

Heart failure (HF) is a progressive clinical syndrome that affects millions of people worldwide and significantly contributes to morbidity and mortality. The condition presents as inadequate blood supply to comply with the body's oxygen requirements because of inefficient heart function. Underlying comorbidities such as hypertension, diabetes, and structural heart disease can cause progressive heart failure.

HF can be divided into three primary categories: heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF). Each type presents unique challenges regarding diagnosis and treatment, necessitating tailored clinical strategies. Pharmacological therapies such as ACE-inhibitors, beta-blockers, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors are essential in the management of heart failure. Non-pharmacological interventions like lifestyle modifications, smoking cessation and dietary management are important. The significance of a multidisciplinary approach, particularly in enhancing long-term outcomes and quality of life in the management of HF are important.

Effective management of heart fHF requires a balance between adherence to clinical guidelines and the provision of individualised care. By integrating evidence-based medicine with comprehensive patient support, healthcare providers can more effectively address the complexities of HF, enabling patients to manage their condition with increased confidence and dignity.

This article examines the fundamental aspects of HF, including its pathophysiology, classification, and symptoms, while underscoring the critical need for early diagnosis and patient-centred care, through a multidisciplinary approach.

Keywords: heart failure, angiotensin-converting enzyme inhibitor, multidisciplinary management

https://doi.org/10.36303/SAPJ.2970

Introduction

Heart failure (HF) significantly contributes to global morbidity and mortality, with an estimated 64.3 million individuals globally impacted.[1,2] Due to its high prevalence and unfavourable clinical outcomes, HF is linked to recurrent hospitalisations and significant healthcare costs.[3,4] Figure 1 depicts the global incidence of heart failure, including the mortality rate. When the syndrome is left untreated or not well managed, the disease is fatal. The rising prevalence of HF in low- and middle-income countries can be attributed to an epidemiological transition alongside a notable increase in the prevalence of contributing factors, including hypertension, diabetes mellitus, dyslipidaemia, and obesity. Additionally, lifestyle changes, characterised by reduced physical activity, heightened alcohol consumption and smoking further exacerbate this issue.[4,5] Currently, there is minimal data regarding the prevalence of HF in Africa due to a lack of sufficient population studies. However, findings from the Heart of Soweto Study cohort (2006),[6] South Africa, revealed that among 1 960 patients diagnosed with HF, 43% experienced incident, or new onset HF, and 23% of these individuals exhibited HF with preserved ejection fraction (HFpEF).[6] In sub-Saharan Africa, hospital-based studies report prevalence rates for HF ranging from 12–33% of adult populations.[6] The overall prevalence of HF in the adult population of developed countries ranges from 1–3%, exhibiting an exponential increase in incidence with advancing age. It affects between 6–10% of individuals aged 65 years and older.[7]

HF is a clinical condition marked by anatomical and functional abnormalities in the myocardium that restrict ventricular filling or ejection of blood. The result of HF is a complex syndrome including fluid build-up and reduced blood flow leading to oxygen deprivation, reduced waste excretion and hypoxaemia in other organs.[1,8]

The objectives of the clinical approach to HF are: (i) accurate diagnosis of the clinical syndrome; (ii) identification and management of the underlying cause; and (iii) implementation of an effective management strategy for symptom control, prolonging survival, and reversing factors that contribute to HF exacerbations.[3,4]

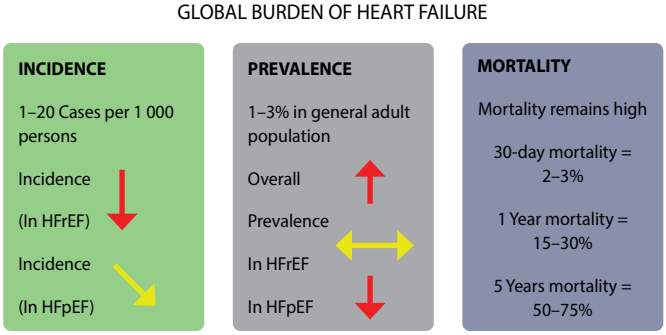

Figure 1: Global burden of heart failure[6]

Pathophysiology and symptoms

HF is a clinical syndrome resulting from structural or functional cardiac abnormalities that impair ventricular filling or ejection, leading to reduced cardiac output and elevated intracardiac pressures. A key component of HF progression is activation of the renin-angiotensin-aldosterone system (RAAS), which promotes vasoconstriction and fluid retention through aldosterone-mediated sodium reabsorption. Concurrent stimulation of the sympathetic nervous system (SNS) increases heart rate and contractility, but chronic activation contributes to myocardial injury, arrhythmogenesis, and adverse remodelling.[9]

Clinically, HF presents with dyspnoea, orthopnoea, peripheral oedema, fatigue, and pulmonary crackles, reflecting elevated filling pressures and inadequate tissue perfusion.[10] Prompt recognition and understanding of these mechanisms is essential for appropriate diagnosis and management.

Classification of heart failure

HF is mainly classified into three different categories, namely heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF).[7] Systolic heart failure, alternatively referred to as HFrEF, is characterised by a left ventricular ejection fraction (LVEF) of less than 40% and systolic dysfunction.[3] Diastolic heart failure, also known as HFpEF, is characterised by impaired left ventricular relaxation, which leads to restricted filling of the left ventricle, while maintaining a LVEF of 50% or greater.[3] HF with preserved ejection fraction is typically a diagnosis of exclusion, often seen in elderly, female, obese patients with a history of hypertension and atrial fibrillation.[2,9,11] HF with mid-range ejection fraction denotes a "grey area," characterised by a mid-range LVEF of 40–49%, possibly indicating the early recovery phase of HfrEF.[2]

Management of heart failure

HF presents a significant global health challenge that necessitates a multidisciplinary approach. Despite recent advancements in pharmacological and interventional therapies, morbidity and mortality rates among these patients continue to be elevated.[12] The major goals of treatment for patients with heart failure according to Inamdar (2016)[8] are to improve the prognosis and reduce mortality, to alleviate symptoms and reduce morbidity by reversing or slowing down the cardiac and peripheral dysfunction. For admitted patients, the goal is to reduce the length of hospital stay and subsequent re-admissions, to prevent organ system damage and lastly to appropriately manage the comorbidities that may contribute to poor prognosis.[8]

Effective management of HF poses a significant challenge for cardiologists.[13] The complexity of this condition, combined with the growing number of available pharmacological treatments, necessitates standardised approaches to enhance the effectiveness of HF therapy in reducing mortality and re-hospitalisation rates.[13] It necessitates a comprehensive approach that includes pharmacological treatments, lifestyle changes, device interventions and collaborative multidisciplinary care.[1,14,15] The European Society of Cardiology (ESC) has developed guidelines by evaluating the evidence level and the strength of recommendations for specific management options and categorised them based on established criteria as outlined in Table I.[15]

Table I: Classes of recommendations, adopted from ESC[15]

Class	Definition	Wording to use
1	Evidence and/or general agreement that a given treatment option is beneficial, useful and effective.	Recommended/ Indicated
2	There is conflicting evidence about the efficacy of the treatment or procedure.	
2a	The weight of the evidence is in favour of usefulness or efficacy	Should be considered
2b	There is less evidence to support the efficacy of the treatment.	May be considered
3	The evidence or general agreement that the given treatment or procedure is not useful or effective and in some cases may be harmful.	Not Recommended

Treatment with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) has led to a significant improvement in the prognosis of heart failure patients.[16] The current guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) recommend initiating treatment with

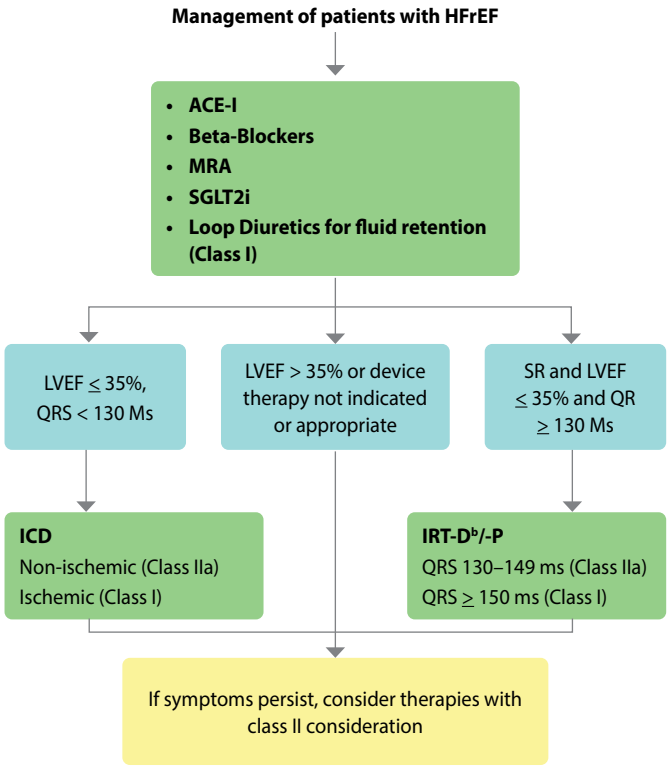

Figure 2: ESC 2021 therapeutic algorithm of Class I Therapy Indications for a patient with heart failure with a reduced ejection fraction[15]

angiotensin-converting enzyme inhibitors/angiotensin receptor blockers ± neprilysin inhibitors (ACE-I/ARNI), a combination of angiotensin receptor blocker and neprilysin inhibitor to treat specifically HFrEF. βeta-blockers (BB), mineralocorticoid receptor antagonists (MRAs), and sodium glucose cotransporter-2-inhibitors (SGLT2i) additionally lower the risk of mortality and hospitalisation in patients with heart failure with reduced ejection fraction.[13]

The main goal of these medications is to alleviate symptoms, reduce fluid retention, and improve heart function.[17] Patients with HFrEF should participate in a disease management programme, managed by a multidisciplinary team. A variety of treatment options are available, and patients should be regularly assessed for their eligibility for each treatment modality, as shown in Figure 1.[18]

The goals of therapeutic therapies for heart failure with preserved ejection fraction (HFpEF) are to manage comorbidities, avoid disease progression, enhance quality of life, and reduce symptoms. The mainstays of treatment include dietary changes, exercise, weight loss, and reduced sodium intake (table salt). A blood pressure target of less than 130/80 mm Hg is advised for antihypertensive treatments, such as diuretics, ARNIs, ARBs, and MRAs. It has been demonstrated that beta-blockers, sacubitril-valsartan, and sodium-glucose cotransporter-2 inhibitors (SGLT2i) are advantageous.[19] The treatment of heart failure I patients with preserved ejection fraction heart failure is summarised in Figure 3.[20] (Refer to Table I for explanation of the strength of recommendations)

The role of the pharmacist in management of heart failure

Pharmacists play an important role in the multidisciplinary management of heart failure by optimising medication therapy, enhancing adherence, and reducing hospital readmissions. Their involvement in medication reconciliation, especially during transitions of care, helps prevent errors and ensures continuity of treatment. Pharmacists, being the custodians of medication, often have information on latest guidelines and new treatment modalities and should provide that information to other members of the multidisciplinary team. They provide patient education on proper medication use and lifestyle changes, empowering patients to manage their condition more effectively. Pharmacists can monitor patient adherence and stress the importance of adherence of their treatment regimens. Through collaborative care, pharmacists contribute to improved therapeutic outcomes, greater patient satisfaction, and increased self-care ability. As treatments for heart failure evolve, the role of pharmacists continues to expand, reinforcing their value in chronic disease management.[21,22]

Schumacher et al. (2021)[23] found through the results of their systemic review that pharmacist care in a clinic setting can improve patient knowledge on their condition, medication adherence, and optimise symptom control. When the complexity of guideline-directed management of conditions like HF is considered, the pharmacist is in a unique position to focus on medication management and patient education, which is a necessary part of the management strategy for these vulnerable patients.[23]

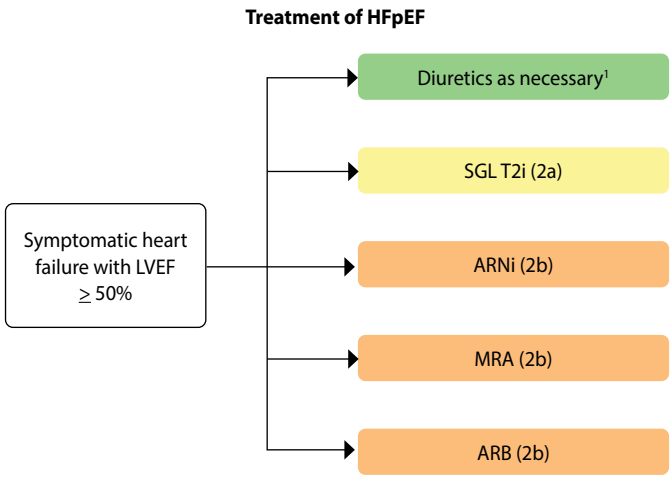

Figure 3: Recommendations for patients with LVEF (≥ 50%)

Conclusion

HF, a clinical syndrome with underlying comorbidities like hypertension, diabetes and structural heart disease, globally still contributes significantly to morbidity and mortality. The management of HF treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has led to a significant improvement in the prognosis of HF patients. Pharmacists, as part of the multidisciplinary team, can make a positive impact on the management of HF patients. Pharmacists contribute by doing medication reconciliation and stressing the importance of adherence. Pharmacists may further monitor symptom control and provide education to patients. Pharmacists continue expanding their roles to meet the demands, reduce medication-related costs, and improve quality of care for cardiac patients in an ever-changing healthcare system.

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Human papillomavirus (HPV) as the main cause of cervical and other related cancers: a review

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Abstract

Human papillomavirus (HPV) is a major cause of several cancers, most notably cervical cancer, which is the fourth most common cancer in women worldwide. HPV infections are typically spread through skin-to-skin contact during sexual activity, and while most infections are cleared by the immune system without symptoms, persistent infection with high-risk strains, such as HPV-16 and HPV-18, can lead to cellular changes in the body. These changes, over time, can result in precancerous lesions and, if untreated, progress to invasive cancer. Human papillomavirus (HPV) is a prevalent sexually transmitted infection recognised as the primary cause of cervical cancer, as well as other malignancies such as anal, oropharyngeal, penile, vulvar, and vaginal cancers. Recent advancements in HPV vaccines, including broader protection against multiple strains, have significantly contributed to reducing the incidence of HPV-related cancers. This review explores the role of HPV in oncogenesis, focusing on its types, mechanisms, and contribution to various cancers. Current prevention strategies, including vaccination, screening, and treatment options, are also discussed. The article emphasises the importance of widespread vaccination and early detection to reduce the global burden of HPV-associated cancers.

Keywords: Human papillomavirus, sexually transmitted infection, cervical cancer

https://doi.org/10.36303/SAPJ.1164

Introduction

Human papillomavirus (HPV) is a group of over 100 related viruses, many of which infect the skin and mucous membranes of humans.[1] It is the most common sexually transmitted infection globally, affecting both men and women. HPV is primarily transmitted through direct skin-to-skin contact during sexual activity.[1] While many HPV infections are harmless and clear up on their own without causing symptoms, certain high-risk strains, particularly HPV-16 and HPV-18, can lead to serious health problems, including cervical cancer, as well as cancers of the anus, throat, vulva, vagina, and penis.[1]

HPV is not only the most common sexually transmitted infection but also a significant global health concern due to its role in multiple cancers. The high prevalence of HPV, especially in sexually active individuals, underscores the need for robust prevention strategies.[2] Apart from cervical cancer, HPV also contributes to other anogenital and oropharyngeal cancers. Globally, cervical cancer cases are predominantly found in low- and middle-income countries, where vaccination and screening programmes are less established. HPV vaccination is vital to lowering this burden and improving access to vaccines in under-resourced areas is a critical public health goal.[2]

Recent studies have expanded on these findings, delving deeper into the mechanisms of HPV-induced carcinogenesis.[3] The authors emphasise the importance of vaccination, early detection, and screening to reduce the global impact of HPV-associated cancers, advocating for a broader, population-based approach to prevention.[4] This call for prevention is echoed in subsequent studies, which highlight the evolving understanding of HPV's oncogenic potential in various anatomical sites.[4] While HPV infection is widespread, progression to invasive cancer is not immediate and depends on additional tumour-promoting factors.[5] This research underscores the importance of understanding these immunological mechanisms to enhance diagnostic accuracy and develop effective immunotherapies for HPV-related malignancies.[5]

Furthermore, research explores the emerging role of HPV in head and neck cancers, particularly oropharyngeal squamous cell carcinoma (OPSCC).[6] Their findings establish HPV as a significant risk factor for these cancers, distinguishing HPV-positive tumours from HPV-negative ones. This emerging recognition of HPV's role in head and neck cancers calls for a broader examination of its oncogenic potential beyond cervical cancer, particularly in light of increasing OPSCC cases globally.[6] These findings collectively highlight the critical importance of vaccination, early detection, and the development of immunotherapies in reducing the global burden of HPV-associated cancers. The literature from 2020 to 2024 reflects a growing recognition of HPV's impact across a range of cancers and underscores the need for comprehensive public health strategies.

In addition to its association with cancer, low-risk HPV strains can cause genital warts and other benign lesions.[1,2] Preventive measures, such as the HPV vaccine, have proven effective in reducing the risk of infection from the most dangerous strains.[1] Vaccination programmes, alongside routine screening like Pap smears for women, play a crucial role in early detection and prevention of HPV-related diseases.[2] A Pap smear is a procedure where cells are removed from the cervix for testing.[2]

Cervical cancer is the fourth most common cancer among women worldwide, with more than 90% of cases attributed to human papillomavirus (HPV) infection.[1] The primary cause of many epithelial lesions and cancers, primarily on cutaneous and mucosal surfaces, is the HPV.[2] Those who have multiple sexual partners and/or persistent HPV infection are particularly vulnerable to acquiring additional HPV subtypes.[2]

Understanding the relationship between HPV and cancer is critical for developing effective prevention, screening, and treatment strategies.[7] This review explores the role of HPV in the pathogenesis of cervical and other cancers, emphasising the need for global awareness and vaccination.

HPV and cancer development

HPV overview

HPV is a deoxyribonucleic acid (DNA) virus from the Papillomaviridae family, with over 200 identified types.[8] These types are categorised into "low-risk" and "high-risk" groups based on their oncogenic potential.[8] Low-risk types, such as HPV 6 and 11, are associated with benign conditions like genital warts, while high-risk types, particularly HPV 16 and 18, are implicated in cancer development.[8]

HPV primarily infects epithelial cells, leading to changes in the cell cycle and immune evasion.[9] Persistent infection with high-risk HPV types can cause cellular mutations and the progression to malignancy.[9]

Mechanisms of oncogenesis

The recent literature provides a comprehensive examination of human papillomavirus (HPV) as a necessary cause of cervical cancer and its association with other malignancies, such as anal, vulvar, vaginal, and penile cancers. Recent studies synthesise evidence on the critical role of HPV in oncogenesis, particularly its increasing prevalence in oropharyngeal cancer among younger adults.

HPV remains a critical factor in the aetiology of various cancers, particularly cervical cancer, which continues to be a significant global health issue.[4]

The pathogenesis of HPV is complex, involving intricate molecular mechanisms that lead to oncogenesis.[5] Research elucidated these mechanisms, particularly in cervical and other anogenital cancers. They highlighted the ongoing disparities in disease burden between high- and low-income countries, emphasising the need for enhanced public health initiatives and the development of innovative screening technologies to enable early detection and timely treatment.[5]

Recent research has expanded the understanding of HPV's impact beyond cervical cancer, notably in oropharyngeal squamous cell carcinoma (OPSCC). Research has shown that HPV-positive OPSCC cases tend to have better prognoses than HPV-negative cases, indicating the need for differentiated treatment strategies.[6]

Furthermore, advances in HPV genotyping have been identified as essential in improving prevention strategies, particularly through earlier diagnosis and more targeted interventions.[6]

The role of immunisation in preventing HPV infections remains a central focus in public health research. Research emphasised the effectiveness of prophylactic vaccines, advocating for gender-neutral vaccination campaigns to enhance herd immunity and reduce HPV-related diseases.[10] In addition, researchers explored therapeutic interventions for HPV-associated cervical lesions, highlighting the growing potential of immunotherapy in treatment protocols.[11]

Moreover, the epidemiology and molecular pathogenesis of HPV-related cancers have been further explored in recent years, particularly concerning immune evasion mechanisms employed by the virus. Researchers have provided insights into how understanding these mechanisms can inform the development of more effective vaccines and public health strategies.[12] Computational models simulating HPV transmission and prevention strategies have further emphasised the importance of addressing persistent oncogenic HPV infections to prevent cervical cancer progression.[13] Together, these advancements underscore the importance of vaccination, early detection through innovative screening methods, and targeted treatments in reducing the global burden of HPV-associated diseases.

HPV infection induces cancerous transformation primarily through its E6 and E7 oncoproteins, which disrupt the cell's normal regulatory pathways. E6 leads to the degradation of the p53 tumour suppressor protein, while E7 inactivates retinoblastoma protein (pRb).[14] These interactions result in the evasion of apoptosis, uncontrolled cell division, and accumulation of mutations over time. Persistent infection with high-risk strains such as HPV-16 and HPV-18 is most closely associated with cancer development.[14]

In cervical cancer, the transformation from normal epithelial cells to cancerous cells occurs through a series of stages, beginning with infection, progressing to pre-cancerous lesions, and ultimately developing into invasive cancer if left untreated.[14] This process can take several years or even decades, highlighting the importance of early detection.[6]

HPV-related cancers

Cervical cancer

Cervical cancer is the most well-established malignancy caused by HPV.[15] Virtually all cases of cervical cancer are linked to high-risk HPV types, with HPV-16 and -18 responsible for approximately 70% of cases.[15] HPV infects the cells of the cervix, particularly at the transformation zone, where squamous and columnar epithelial cells meet, making this area highly susceptible to viral infection and oncogenic transformation.[15]

The progression from infection to cervical cancer follows a distinct pathway, from low-grade cervical intraepithelial neoplasia (CIN1)

to high-grade CIN (CIN2/3) and, if not treated, to invasive cancer. Regular screening through Pap smears and HPV DNA testing is essential for early detection and treatment of pre-cancerous lesions.[16]

Anal cancer

HPV is responsible for approximately 90% of anal cancer cases, with HPV-16 being the most common type.[17] Anal cancer is more prevalent among individuals with a history of receptive anal intercourse, particularly in men who have sex with men (MSM), and immunocompromised individuals, such as those living with HIV.[17] HPV vaccination has the potential to reduce the incidence of anal cancer, especially in high-risk populations.[17]

Oropharyngeal cancer

HPV is also implicated in a rising number of oropharyngeal cancers, particularly those affecting the tonsils and base of the tongue. HPV-16 is the dominant type associated with these cancers.[18] Oropharyngeal cancer caused by HPV has distinct characteristics compared to those caused by smoking and alcohol, including a younger age of onset and better prognosis.[18] Vaccination against HPV offers a promising strategy for reducing the incidence of HPV-associated oropharyngeal cancers.[18]

Other HPV-related cancers

HPV contributes to approximately 40% of vulvar and vaginal cancers and about 60% of penile cancers.[19,20]These cancers are less common but still pose a significant health burden, particularly in low-resource settings where screening and vaccination rates may be low.[19]

Figure 1 illustatres how HPV is associated with a variety of cancers other than cervical cancer. This figure links HPV to several cancer types, such as anal, penile, valvular, vaginal, oropharyngeal, and colorectal cancers. Panel A in Figure 1 indicates that HPV is the primary causative factor linked to these malignancies; the iceberg theory is used in Panel B to illustrate the disparate percentages of HPV attribution. This depicts that HPV accounts for almost 99% of all cervical cancers and only 50% of penile cancers.

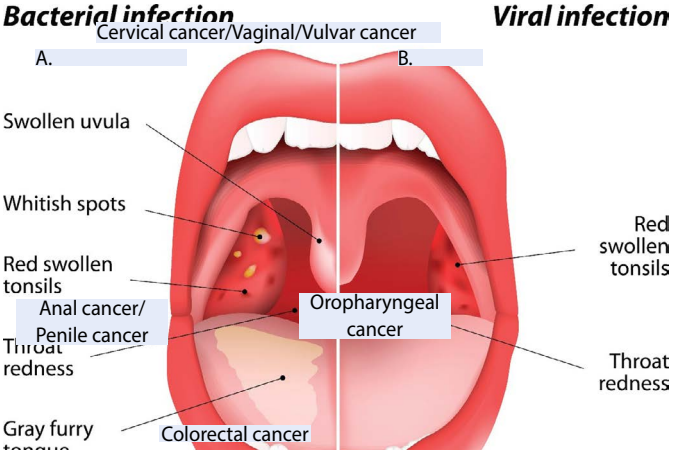

Figure 1: Depiction of HPV-associated malignancies and their prevalence. (A) A major group of malignancies attributed to HPV. (B) Burden of HPV-related malignancies.[20]

Prevention and screening

HPV vaccination

HPV vaccines are the most effective tool for preventing HPV-related cancers.[21] The three available vaccines – Cervarix®, Gardasil®, and Gardasil 9® – target high-risk HPV types, with Gardasil 9 offering the broadest protection against nine HPV types, including HPV-16 and -18. Vaccination is recommended for both males and females, ideally before the onset of sexual activity, but it can still offer protection for sexually active individuals.[21]

The introduction of HPV vaccination programmes has led to significant reductions in the prevalence of high-risk HPV infections and related conditions, such as genital warts and pre-cancerous cervical lesions.[22] However, global vaccination coverage remains uneven, with low-income countries facing challenges related to cost, infrastructure, and public awareness.[22]

Cervical cancer screening

Cervical cancer screening, primarily through Pap smears and HPV DNA testing, plays a crucial role in detecting pre-cancerous changes before they progress to invasive cancer.[23] Regular screening has significantly reduced cervical cancer incidence and mortality in countries with established screening programmes.[23]

HPV DNA testing, which detects the presence of high-risk HPV types, is becoming increasingly common as a primary screening tool.[24] It offers higher sensitivity than Pap smears, particularly in identifying women at risk for developing cervical cancer.[24] Combining HPV testing with traditional cytology (Pap smears) provides an effective approach to early detection.[24]

Screening for other HPV-related cancers

While cervical cancer screening is well-established, screening for other HPV-related cancers, such as anal and oropharyngeal cancers, is less widespread.[25] High-risk populations, such as MSM and individuals with HIV, may benefit from targeted anal cancer screening programmes.[25] Additionally, awareness of HPV's role in oropharyngeal cancers highlights the need for further research on effective screening strategies for this group.[25]

Treatment options for HPV-related diseases

The treatment of HPV-related diseases ranges from managing benign conditions, such as genital warts, to treating precancerous lesions and invasive cancers. The choice of treatment depends on the stage and location of the disease.

1. Treatment of precancerous lesions (Cervical Dysplasia)[20]

- Cryotherapy: This method uses extreme cold to destroy abnormal tissue. It is typically used to treat cervical intraepithelial neoplasia (CIN) and is especially valuable in low-resource settings due to its simplicity and low cost.
- Loop Electrosurgical Excision Procedure (LEEP): LEEP involves using a thin wire loop that carries an electric current to remove abnormal cervical tissue. It is commonly used for moderate to

severe dysplasia (CIN 2 and CIN 3).

- Conisation: This surgical procedure involves removing a cone-shaped section of abnormal tissue from the cervix. It is recommended for women with more severe dysplasia, or in cases where LEEP is insufficient.

2. Treatment of genital warts[20]

Genital warts, caused by low-risk HPV types such as HPV-6 and HPV-11, are typically managed through topical treatments or physical removal methods.

- Topical treatments: Imiquimod and podofilox are commonly used topical medications. Imiquimod stimulates the immune system to fight the virus, while podofilox works by destroying the wart tissue.
- Cryotherapy and electrocautery: Cryotherapy uses liquid nitrogen to freeze and destroy warts, while electrocautery involves burning off the warts with electric current.

3. Treatment of invasive cancer

The treatment of HPV-related cancers, such as cervical, anal, and oropharyngeal cancers, depends on the stage of the disease and may involve a combination of surgery, radiation, and chemotherapy.[26]

- Surgery: Early-stage cervical cancer can often be treated surgically, either through a hysterectomy (removal of the uterus) or conisation. For anal and oropharyngeal cancers, surgery is sometimes used to remove tumours, although these cancers are often treated with non-surgical methods.
- Radiation therapy: Radiation therapy is a mainstay of treatment for advanced HPV-related cancers. It can be used alone or in combination with chemotherapy to shrink tumours and destroy cancer cells.
- Chemotherapy: Chemotherapy is used in more advanced cases or when cancer has spread beyond the primary site. For example, cisplatin-based chemotherapy is commonly used in combination with radiation therapy for the treatment of advanced cervical cancer.
- Targeted therapy and immunotherapy: New treatments, such as immune checkpoint inhibitors (e.g. pembrolizumab), are being explored for HPV-related cancers. These therapies aim to enhance the body's immune response to target and destroy cancer cells. Clinical trials have shown promise in treating HPV-positive cancers, especially in cases where traditional therapies have failed.

The role of a pharmacist

Pharmacists have a significant role in the prevention and treatment of cervical cancer and other cancers associated with the human papillomavirus (HPV). As accessible healthcare professionals, pharmacists are well-positioned to educate the public on HPV, its connection to cancers, and the importance of prevention through vaccination and regular screenings. Pharmacists can promote the uptake of the HPV vaccine by providing counselling, addressing vaccine hesitancy and ensuring that patients understand its role in preventing cervical and other HPV-related cancers, such as anal, oropharyngeal, and genital cancers.[27] In addition, pharmacists can offer support for vaccine administration and adherence to vaccination schedules, particularly for young women and men within the recommended age range.

Pharmacists are essential in ensuring **continuous access to HPV-related treatments and vaccines** by:

- **Managing the supply chain** to prevent stockouts of **HPV vaccines, chemotherapy, and essential supportive care medicines**.
- Working with **health authorities, hospitals, and community pharmacies** to ensure **affordable and equitable access** to medicines.
- Advocating for **cost-effective procurement and distribution strategies**, particularly in **resource-limited settings**.

Pharmacists can advocate for early detection and timely screening, educating patients on the importance of routine Pap smears and HPV testing, which are essential for early intervention. Furthermore, pharmacists assist in the management of treatment for cervical cancer by ensuring patients receive accurate information on prescribed medications, managing side effects and supporting adherence to therapy, including chemotherapy and palliative care. As accessible healthcare professionals in the community, pharmacists can significantly contribute to public health efforts aimed at reducing the incidence and burden of HPV-related cancers.

Conclusion

The human papillomavirus (HPV) is a highly prevalent infection with both benign and serious health implications. While many HPV infections are harmless and resolve without intervention, persistent infections with high-risk strains can lead to various cancers, most including cervical cancer. Preventive strategies, such as vaccination and regular screening, have proven effective in reducing HPV-related cancers and other complications. However, the challenge remains in achieving vaccine coverage and ensuring access to health care, particularly in low-resource settings.

The continued support by pharmacists in public education and vaccination initiatives is essential to control the impact of HPV and reduce the global burden of HPV-related diseases. Pharmacists have an essential role in establishing and developing public health strategies to end HPV. As accessible healthcare professionals, they are instrumental in educating the public about HPV, its link to cancers and the importance of vaccination and screening. Pharmacists can address vaccine hesitancy and ensure adherence to vaccination schedules, particularly for adolescents and young adults. Additionally, they contribute to the management of HPV-related therapies by providing accurate medicine information and supporting treatment adherence. Their involvement in supply chain management ensures continuous access to HPV vaccines and essential therapy, even in resource-limited settings.

By collaborating with other healthcare providers and advocating for equitable access, pharmacists strengthen prevention and treatment strategies, making them a necessary component in the fight against HPV-associated cancers.

Further research is needed to optimise screening strategies for non-cervical HPV-related cancers to improve access to vaccines in low-resource settings. Public health initiatives that are aimed at increasing awareness of HPV and its role in cancer development, alongside the active involvement of pharmacists, will be important in order to achieve prevention and reducing the global impact of HPV-associated cancers.

Conflict of interest

The authors have no conflict of interest.

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Interprofessional impressions amongst 4th-year medical and pharmacy students at Sefako Makgatho Health Sciences University

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Abstract

Background: The function of a multidisciplinary team is to work together to provide patient care; this is facilitated by healthcare professionals from various disciplines joining forces by understanding and respecting each other's roles. The World Health Organization advises that interprofessional education (IPE) be incorporated into the healthcare curriculum as it results in improved patient care and helps students identify each other's roles and perceptions in a multidisciplinary team. The purpose of this study was to investigate interprofessional impressions among 4th-year pharmacy and medical students at a university in South Africa.

Methods: Using a Likert scale, an online survey was conducted on a cohort of 4th-year pharmacy and medical students at the university. The quantitative descriptive data was captured using MS Excel® spreadsheet, and MS Office 365 (2016) and analysis was done using Analysis of Variance (ANOVA).

Results: A response rate of 75.28% was obtained where n = 201 respondents, 76.61% agreed that working together as a multidisciplinary team would benefit patients and improve communication between healthcare professionals. All of the pharmacy students agreed that shared learning will benefit the patient, compared to 2.54% and 5.73% of medical students who disagreed, and strongly disagreed, respectively that working together will ultimately benefit the patient. This difference in perception highlights a potential gap in understanding the roles of different healthcare professionals, underscoring the need for interprofessional education to foster mutual respect and collaborative practice.

Conclusion: This study highlights a clear need for IPE within the healthcare curriculum, particularly among 4th-year pharmacy and medical students. The findings demonstrate that while a majority of students acknowledge the benefits of working together in a multidisciplinary team, there is a disparity in perceptions between the two groups. Pharmacy students unanimously recognised the value of shared learning for improved patient outcomes, whereas a small but notable proportion of medical students expressed scepticism regarding its benefits.

Keywords: interprofessional education; interprofessional impressions; pharmacy; medicine; collaborative learning; professional roles

https://doi.org/10.36303/SAPJ.1209

Introduction

Interprofessional impressions may be defined as perceptions or attitudes that exist between two or more professions, such as pharmacists working with medical doctors or nurses.[1,2] Perception and attitudes may contribute greatly to effective communication between healthcare professionals. If communication among healthcare professionals is diminished, patients are subjected to poor outcomes, which may include delayed treatment, misdiagnosis, medication error, patient injury or even death.[3,4] Furthermore, current research shows integrative reviews which suggest that healthcare professionals are trained differently and separately, therefore, they exhibit different communication skills.[4] IPE is a platform that allows students from different professions to learn together and integrate acquired knowledge to better understand their roles and other professions' roles in a multidisciplinary team setting. It helps bring proficiency in a collaborative setting where healthcare professionals share information and skills.[5] Understanding each other's roles helps reduce clinical errors and ensure the best care for patients.[6,7]

University-based health professional training largely occurs in discipline-explicit silos. Sefako Makgatho Health Sciences University (SMU) is not an exception; each profession's teaching needs to occur interdependently, and this will contribute positively towards how healthcare professionals view each other's roles in the healthcare setting.[6] Pharmacists and medical doctors were found to have perceptions about each other's roles and responsibilities in the healthcare system, which contributed to the effectiveness of their communication.[8] In a healthcare setting, patients are not attended to by only one healthcare professional; they are attended to by doctors, pharmacists and other healthcare professionals. There is a need for interprofessional education in the curriculum since they will be working together in the workplace. Therefore, the rationale of this quantitative descriptive study is to evaluate the interprofessional impressions of pharmacy and medical students, how they perceive each other's roles, and to determine if there is a need for IPE amongst pharmacy and medical students at SMU. The objectives of the study were set out as follows: to determine the 4th-year medical and pharmacy students' impressions regarding each other's role as healthcare

professionals and to determine the perceived need for IPE amongst pharmacy and medical students.

Materials and methods

A survey adapted and adopted from McFadyen et al.[9] was conducted on a cohort of 4th-year pharmacy and medical students at SMU using a Likert scale. A pilot study was conducted on 3rd-year pharmacy and 5th-year medical students to assess the feasibility and validity of the study. This took place from 14–17 September 2020. The primary aim of the pilot study was to assess the feasibility and validity of the survey in terms of clarity of instructions, technical functionality, and estimated completion time. The data collection instrument consisted of 19 questions aimed to determine the perceived need for shared learning among the students and their interprofessional impressions of each other. The questions were divided into four categories as follows: shared learning and associated self-improvement, goals of a multidisciplinary team, perceptions and readiness for interprofessional education and student knowledge of their professional roles. The quantitative descriptive data was captured using MS Excel® spreadsheet, and MS Office 365 (2016) and analysis was done using ANOVA.

A method developed by Shona McCombes[10] using the four steps was adopted and adapted: (1) Explanation of the methodological approach; (2) Description of methods of collecting data; (3) Description of data analysis; and (4) Evaluation of methodological choices.

Methodological approach

The main research question was to investigate the interprofessional impressions among 4th-year pharmacy and medical students. This was to provide insight into how pharmacy and medical students perceive each other's roles and the need for IPE. The data was collected through a quantitative descriptive study design. The principle of quantitative descriptive analysis is based on the measurement of specific attributes of a population, often using a scale, in a reproducible manner to yield a comprehensive quantitative description amenable to statistical analysis. The study made use of convenient sampling by including all registered 4th-year pharmacy and medical students at SMU during the year 2020. The targeted number of participants from the study population was 53 pharmacy and 214 medical students (N = 267), with inclusion criteria being 4th-year pharmacy and medical students studying at SMU and registered for the year 2020. The exclusion criteria were other disciplines studying at SMU including Allied Health and Nursing students and invited students who were not interested in participating.

Methods of collecting data

After obtaining ethical clearance, SMUREC Ethics Reference Number, SMUREC/P/71 /2020:UG, a pilot study was conducted on 3rd-year pharmacy and medical students to assess the feasibility of the study. This took place from 14–17 September 2020. An online platform, Google Forms® was used to collect data; this was then followed by data collection from 21–25 September 2020. The survey was conducted virtually, where a link to the Google Form® was sent to the respective groups. The survey had a brief background about the study, informed consent and instructions. The survey included the participant's demographic details (age, gender, and ethnicity), the programme of study and prior experience with IPE. The survey took the form of a Likert scale with answers ranging from "strongly disagree to strongly agree" denoted by numbers 1 to 5, respectively. Participants were allowed a week to respond.

Data analysis

Data were analysed using descriptive statistics, including frequencies, percentages, mean and standard deviation. ANOVA was also used, which involved comparing variances from two data sets. Data was captured on an MS Excel® spreadsheet, MS Office 365 (2016). Descriptive and inferential data analysis was done on the quantitative data, including the participants' demographics. Quantitative data was captured on Microsoft Excel®, and MS Office 365 (2016) and analysed using Stata V15 statistical analysis software. Frequency tables were used to summarise the trends.

Evaluation of methodological choices

Data was collected and generated in a way that is fair and not harmful to the participants. For instance, an agreement Likert scale questionnaire was used which offered respondents a reasonable range (five options) of answers to choose from. The method was appropriate for fulfilling the overall aims of the study because the population size was sufficient, N = 267 (53 pharmacy and 214 medical students); this allowed researchers to generalise and make recommendations based on the findings.

Results

A response rate of 75.28% was obtained; this was deemed satisfactory and representative. Respondents included 157 medical students and 44 pharmacy students, denoting 73.36% and 83.01%, respectively. Questions were categorised based on similarity in concepts aimed to investigate respondents. Four categories, as detailed below, were derived and these guide the results and discussion of the findings.

a. Students' perspectives on shared learning about self-improvement.
b. Students' understanding of the goal of a multidisciplinary healthcare team.
c. Students' perceptions about learning together before qualification.
d. Students' knowledge about their professional roles and other professions' roles.

Demographics and educational background information

Results show that 67% were females and 31% were males, 83.16% were African and 7.92% were Whites, 5.94% were Indians and 2.47% were Coloured, 1.48% were aged 16–20, 85.14% were

aged 21–25, 12.37% were aged 26–30 then 0.49% was aged 30 and above. Of the 201 respondents, 26 had previously obtained a qualification, and the majority had a Bachelor of Science degree. A total of 107 medical and 16 pharmacy students indicated that IPE was not offered in their curricula; more than half of the respondents, 61.19%, shared this viewpoint.

Students' perspectives on shared learning about self-improvement

In this category of questions 80.09% were positive (Figure 1), where respondents either agreed, or strongly agreed that shared learning with other disciplines would help individuals become more effective members of a healthcare team, 79.6% were positive that it would help them understand clinical problems, 84.57% were certain that it would help them think positively about other professions and only 76.11% students think that it would help them understand their limitations and become better team workers. Similarly, there is a finding in a study done by Larivaara & Taanila in 2004 where interprofessional collaboration assisted doctors in finding solutions for challenging patient problems and understanding the value and roles of other healthcare professionals.[11] Therefore, it was unsurprising that most students from both disciplines strongly agreed that shared learning would positively impact individuals' self-improvement. Based on the results, it was deduced that students understand the relevance and importance of shared learning as part of the curriculum.

Students' understanding of the goal of a multidisciplinary healthcare team

Out of 201 respondents, 76.61% either agreed, or strongly agreed that working together would benefit patients, and 77.61% were certain it would help clarify the nature of patient problems as seen in Figure 2. While none of the pharmacy students disagreed, 2.54% and 5.73% of medical students disagreed, and strongly disagreed respectively that working together will ultimately benefit the patient. In both disciplines, 82.08% of students either

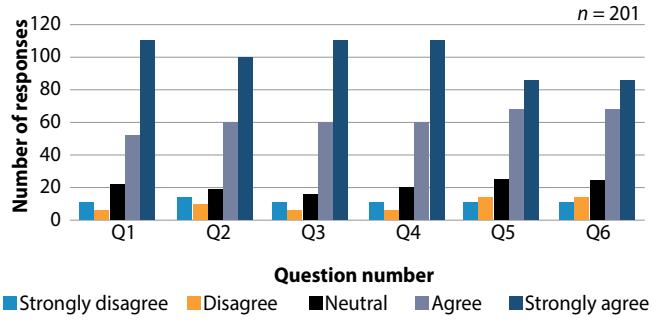

Figure 1: A summary of students' perspectives on shared learning about self-improvement based on Questions 1, 3, 4, 6, 9 and 16

Key: Q1 – Learning with other students will help me become a more effective member of a healthcare team; Q3 – Shared learning with other medical and pharmacy students will increase my ability to understand clinical problems; Q4 – Learning with medical and pharmacy students before qualification would improve relationships after qualification; Q6 – Shared learning will help me to think positively about other professionals; Q9 – Shared learning will help me to understand my limitations; and Q16 – Shared learning before qualification will help me become a better team worker.

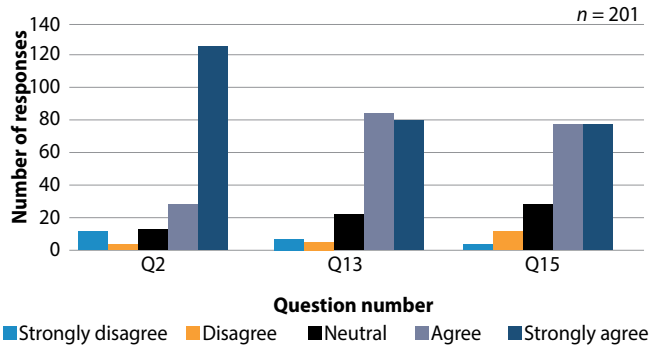

Figure 2: A summary of students' understanding of the goal of a multidisciplinary healthcare team based on Questions 2, 13 and 15

Key: Q2 – Patients would ultimately benefit if medical and pharmacy students worked together to solve patient problems; Q13 – Shared learning with medical and pharmacy students will help me to communicate better with patients and other professionals; and Q15 – Shared learning will help to clarify the nature of patient problems.

agreed, or strongly agreed that learning together would improve communication among healthcare professionals and patients. This agrees with a study that was done by Illingworth & Cheivanayagam in 2007 that interprofessional education improved trust and enhanced communication, leading to changes in the attitudes that professionals may have towards each other.[12]

Students' perceptions about learning together before qualification

Results show that 89.55% of the 201 respondents were positive that it is necessary to effectively communicate with each other as professionals (Figure 3). About 89.05% reported that it is important to trust and respect each other in small-group learning. A majority, 85.57% reported that it is important to have team working skills. Collaborative learning was not deemed to be a 'waste of time' as reported by the majority (78.10%) of the respondents. A large portion, 69.65% of respondents were positive that clinical problem-solving skills could be learned with students from different departments. A majority, 80.09%, were willing to work on small group projects with each other. A study published in 1997 by Tanskanen et al., revealed that pharmacists and doctors had a controversial perception of each other's roles and responsibilities, and this negatively affected their communication and ability to work as a team.[8] This was congruent with the current study findings as about five medical students were of a viewpoint that interprofessional education will not assist them in clinical problem-solving skills.

Students' knowledge about their professional roles and other professions' roles

As observed in Figure 4, 70.14% of both medical and pharmacy students either disagreed or strongly disagreed that they were not sure of their roles in an interprofessional group simply meaning they understood their roles. Interestingly, the emergence of "neutral" as an answer for question 17 was observed, which tells us that students were not sure whether other healthcare professionals' functions were to support doctors or pharmacists. It was also noted that 54.77% of medical students agreed that

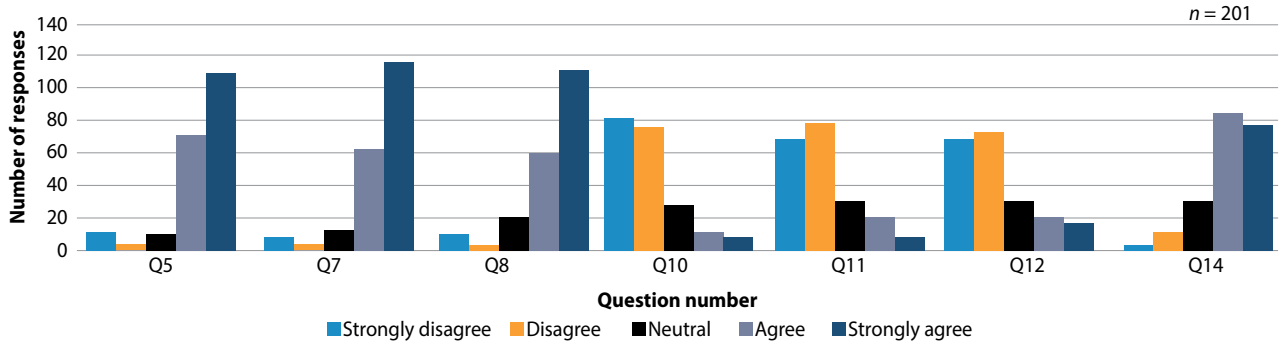

Figure 3: A summary of students' perceptions about learning together before qualification based on Questions 5, 7–8, 10–12 and 14

Key: Q5 – Communication skills should be learned with medicine and pharmacy students; Q7 – For small-group learning to work, students need to trust and respect each other; Q8 – Team-working skills are essential for medical and pharmacy professionals to learn; Q10 – I don't want to waste my time learning with medical and pharmacy students; Q11 – It is not necessary for undergraduate medical and pharmacy students to learn together; Q12 – Clinical problem-solving skills can only be learned with students from my department; and Q14 – I would welcome the opportunity to work on small-group projects with other medicine and pharmacy students.

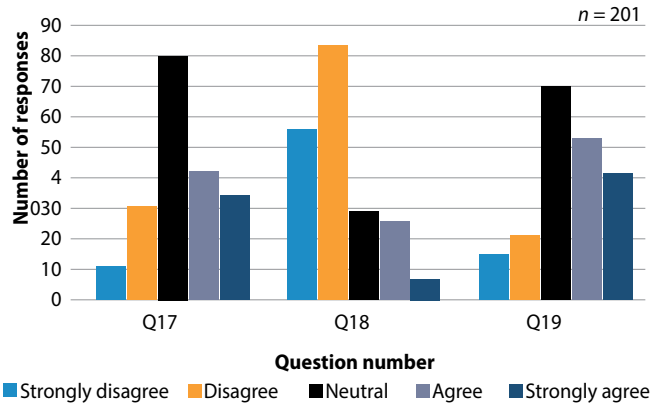

Figure 4: A summary of students' perceptions about learning together before qualification based on Questions 17–19

Key: Q17 – The function of medicine/pharmacy and therapists is mainly to provide support for doctors/pharmacists; Q18 – I'm not sure what my professional role will be; and Q19 – I have to acquire much more knowledge and skills than other medical/pharmacy students.

they were expected to learn more than other disciplines while pharmacy students were neutral about the notion, and it can be assumed that they were unsure. This shows clearly that some students were not certain if they understood different professional roles in interprofessional groups. This gap of knowledge can be filled by introducing IPE earlier in the curriculum of both pharmacy and medical students. It would, however, be justifiable for 4th-year medical students not to understand their professional roles in interprofessional groups since they would not have been exposed to IPE as per the current curriculum at the institution. The findings of this study are congruent with the previous outcomes of a study by Oxelmark,[13] who reported that medical students lack knowledge about the roles of other healthcare professionals and only realise their professional responsibilities after learning together. Pharmacy students, on the other hand, had been exposed to IPE during the first week of their final year studies together with other disciplines such as nursing, physiotherapy and dentistry.

Discussion

The current study answers if medical and pharmacy students have IPE included in their curriculum, and their willingness to be part of IPE and it answers the question regarding their interprofessional impressions of each other. Before this study, only a few studies had been done on interprofessional impressions among pharmacy and medical students. However, studies done previously focused on interprofessional impressions amongst other disciplines. For example, in 2015 Wilbur and Kelly at the Qatar University College of Pharmacy and the University of Calgary used a focus group including pharmacy and nursing students that covered similar objectives as the current study.[3]

The findings of this study demonstrate that IPE is not formally integrated into the curriculum for medical and pharmacy students at SMU. Although an IPE programme exists for final-year students across health sciences, medical students have not participated due to timetable misalignment and logistical challenges. This has led to a perception among some students that IPE is absent from their curriculum. Despite this, the survey reveals that students from both disciplines recognise the importance of learning together and view each other as valuable collaborators in patient care.

These findings are significant within the context of South Africa's National Health Insurance (NHI), where the Contracting Unit for Primary Health Care (CUP) is envisioned as the primary service delivery model. Effective CUP delivery requires cohesive, multidisciplinary teams, a goal that can be achieved through structured IPE. IPE fosters teamwork, improves communication, and clarifies professional roles, ultimately enhancing patient outcomes and service efficiency. In the absence of IPE, students may develop incomplete perceptions of each other's roles, which can hinder future collaboration.

The study also suggests that the lack of IPE may have influenced the differing perceptions between medical and pharmacy students. While most respondents recognised the importance of IPE and expressed willingness to engage in shared learning, their actual exposure to it was limited. This highlights the need for SMU

to prioritise structured, curriculum-based IPE, ensuring that all health science students gain practical experience in collaborative practice. Given the findings, future research should explore interprofessional perceptions among other disciplines, such as pharmacy and nursing or dentistry students, to provide a broader understanding of interprofessional dynamics in healthcare education.

Limitations and recommendations for future studies

The study was initially designed to be conducted using self-administered questionnaires. However, due to the COVID-19 pandemic, the survey was conducted via Google Forms®. Consequently, the target population was reduced from 53 pharmacy students and 214 medical students to 44 pharmacy and 157 medical students. While this may have impacted the study's robustness, it remains both feasible and reproducible, as a response rate of ≥ 75% was achieved.

The use of an online survey may have inadvertently excluded students with limited internet access or those less engaged with digital platforms, potentially leading to participation bias. Additionally, the study was limited to 4th year pharmacy and medical students at a single university in South Africa, restricting the generalisability of the findings to other institutions and healthcare settings. Furthermore, the exclusion of other key healthcare disciplines, such as nursing, physiotherapy, and occupational therapy, means that the study does not fully capture a comprehensive multidisciplinary perspective. A truly holistic approach requires input from a broader range of healthcare professionals. Despite these limitations, the findings indicate that most pharmacy and medicial students recognise the value of IPE.

The survey format did not allow participants to fully articulate their impressions of each other's professions, as it relied exclusively on close-ended Likert scale questions. This format may have introduced social desirability bias, where students selected more favourable responses to align with perceived norms rather than their actual opinions. Additionally, the study relied solely on quantitative data, lacking qualitative insights (e.g. open-ended responses or interviews), which may have provided a deeper understanding of why some students expressed reservations about interprofessional collaboration.

To enhance future research, the following recommendations are proposed: (i) incorporating more qualitative studies to allow students to express their perspectives in greater depth; (ii) expanding the study to include multiple universities and a wider range of healthcare disciplines; (iii) integrating qualitative research methods, such as focus groups or interviews, to explore the underlying factors influencing students' perceptions; and (iv) conducting a longitudinal study to track changes in interprofessional attitudes over time.

Conclusions

The survey results indicate a generally positive perception of IPE among students, with most respondents strongly agreeing on its importance. However, notable differences in perceptions were observed between the two groups. While the majority of pharmacy students expressed confidence in their ability to contribute effectively within a multidisciplinary team, a smaller proportion of medical students viewed the inclusion of pharmacy students as critical to patient outcomes. This disparity suggests a potential gap in understanding the roles of different healthcare professionals, highlighting the importance of interprofessional education to promote mutual respect and collaborative practice.

Overall, the findings emphasise the need for structured, curriculum-based interprofessional education to enhance mutual understanding, respect, and teamwork among future healthcare professionals. Integrating shared learning experiences for pharmacy and medical students is recommended to prepare them for effective collaboration in clinical settings.

Acknowledgements

The authors wish to acknowledge all of the students who assisted in data collection, namely: LH Mabotha, TR Malatji, MP Shikoane, TE Mokonyema and R Rankeng.

Conflicts of interest

The authors declare no conflict of interest.

Funding source

This research received no external funding.

Ethical approval

Ethics approval was obtained from the Sefako Makgatho University Research Ethics Committee, Ethics Reference Number, SMUREC/P/71 /2020:UG.

Informed consent was obtained from all subjects involved in the study

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Full list of references available on request

Pharmaceutical Practitioner

South African Association of Community Pharmacists

PIMART – An Innovative Solution for Enhancing HIV Healthcare and Supporting National HIV Initiatives in South Africa

Jameel Kariem

Abstract

Pharmacist-Initiated Management of Antiretroviral Therapy (PIMART), if implemented, could be a beneficial and complimentary strategy to expand HIV care in South Africa. This is especially so in underserved communities. With the comprehensive PIMART curriculum and training, along with policy support from regulators, pharmacists can enhance access to PEP, PrEP, and first-line ARVs. The objectives of PIMART also align with South Africa's National Strategic Plan (NSP) 2023–2028 for HIV, Tuberculosis (TB), and Sexually Transmitted Infections (STIs). Both programmes support decentralised, integrated, and equitable care. Resolving the legal case between the Independent Practitioners Association Foundation (IPAF) and the South African Pharmacy Council (SAPC), strengthening regulatory support, and leveraging digital tools to scale up PIMART, are key factors to ensure full implementation. Key implementation strategies like policy reforms, continuous pharmacist training, digital health integration, community engagement, financial support, and strong monitoring systems, are necessary to ensure the rollout of PIMART is maximised. This will support service delivery and improve clinical effectiveness. A coordinated, multisectoral approach will enable pharmacists to contribute even further to South Africa's HIV response and the achievement of the UNAIDS 95-95-95 targets.

https://doi.org/10.36303/SAPJ.3090

Introduction

PIMART is a transformative approach to expanding Human Immunodeficiency Virus (HIV) healthcare access, particularly in resource-limited settings. PIMART-trained pharmacists can contribute and play a crucial role in bridging the gap in HIV healthcare access. With their training, and policy support from stakeholders, pharmacists can significantly enhance access to key medications for Post Exposure Prophylaxis (PEP), Pre Exposure Prophylaxis (PrEP), and first-line (Anti-Retroviral) ARVs. This document outlines the strategies for expanding PIMART services in communities, including additional services like virtual consultations, and the use of digital tools. The collaborative efforts of PIMART and the National Strategic Plan (NSP) 2023–2028 for HIV, Tuberculosis (TB), and Sexually Transmitted Infections (STIs), which share similar objectives, could contribute significantly to South Africa reaching the UNAIDS target of 95-95-95. Furthermore, it is proposed that by implementing PIMART, there are potential direct and indirect benefits in the fight against HIV, like increased diagnosis and early ART initiation, and reduced state facility healthcare congestion.[11]

About PIMART

PIMART is an expanded scope of practice for pharmacists in South Africa, approved by the South African Pharmacy Council (SAPC). The course was designed as such that PIMART trained pharmacists, who have completed the required supplementary training, and registered with the South African Department of Health, may start PrEP, PEP and first line ART, as well as the initiation of Tuberculosis Preventative Therapy (TPT). Upon successful completion of the PIMART course, the Director General (DG) of Health would issue a Section 22A (15) permit, which would then be recorded with the SAPC, allowing PIMART trained pharmacist to practice. A primary qualifying criterion for the treatment of HIV with first line ART is that PIMART trained pharmacists may only treat uncomplicated non-immunocompromised HIV positive people, 15 years and older. This is to ensure that PIMART trained pharmacists operate within their scope of practice.

However, a recent court battle between a group of private medical doctors (IPAF) and the SAPC, has put the implementation of PIMART on hold.[1, 2, 3]

Some HIV statistics from the Western Cape Department of Health

Regions of South Africa face unique challenges in delivering effective HIV services. At the end of March 2023, it was estimated that approximately 531 021 people in the Western Cape are living with HIV, with around 500 263 knowing their HIV status (94%) and approximately 340 058 (68%) currently on treatment according to the Western Cape Department of Health's (WCDOH) Provincial Implementation (PIP) plan for HIV, TB and STI's for the NSP 2023 – 2028.

For 2024, the Western Cape, with a population of 7,4 million had just over 500,000 people living with HIV (PLHIV), and just over 54,000 diagnosed with Tuberculosis (TB). The 95-95-95 cascade as at 2024 was 73.4% on ART and 89% virally supressed. This means that the Western

Cape has achieved the first target, with 95% of PLHIV aware of their status. However, only 73.4% of those diagnosed are on ART, falling short of the second target. Among those on ART, 89% have achieved viral suppression, which is close to the third target. The data shows that the province has made notable progress in awareness and viral suppression. However, there is a need to enhance linkage to care and retention in treatment to achieve the 95-95-95 goals.

While government initiatives are being implemented to enhance the accessibility and efficacy of PEP, PrEP, and first-line ART in South Africa, persistent challenges pertaining to healthcare infrastructure, patient education, and adherence support will need be addressed to improve HIV prevention and treatment outcomes within these communities.[14]

PIMART and the National Strategic Plan (NSP) 2023- 2028 for HIV, TB and STIs

The PIMART program and South Africa's National Strategic Plan (NSP) 2023–2028 for HIV, Tuberculosis (TB), and Sexually Transmitted Infections (STIs), share several key similarities, reflecting a unified approach to combating these epidemics.

The NSP 2023-2028, serves as South Africa's comprehensive framework to eliminate HIV, TB and STIs, as public health threats by 2030. One of its core objectives is to maximize equitable and equal access to services and solutions for HIV, TB, and STIs. The NSP 2023-2028, and the PIMART initiative, are integrally connected through their objectives to broaden access to HIV treatment and enhance the delivery of healthcare services.

A key goal of the NSP is to break down barriers to achieving solutions for HIV, TB and STIs, with the objective of strengthen community-led responses. The PIMART initiative aligns with this objective by enabling trained pharmacists to initiate and manage ART, including PrEP and PEP in their communities. This approach decentralizes HIV services, making them more accessible, especially in underserved areas.[12]

Some of the key connections between the NSP and PIMART

The NSP 2023-2028 aims to ensure universal access to HIV prevention and treatment services to achieve the UNAIDS 95-95-95 targets. PIMART supports this goal by allowing trained pharmacists to initiate ART for eligible patients.

The NSP 2023-2028 underscores the importance of expanding task-shifting and integrating HIV services into primary healthcare to alleviate the burden on other healthcare professionals and clinics. PIMART can contribute to this effort by enabling pharmacists to administer ART, PrEP, and PEP in their pharmacies, thereby decreasing pressure on conventional healthcare facilities.

The NSP 2023-2028 promotes community-based service delivery models to make HIV and TB care more accessible. PIMART can contribute by allowing pharmacies to serve as additional points of care, providing HIV testing and treatment closer to where people live and work.

The NSP 2023-2028 aims to improve early diagnosis and prompt treatment for HIV patients. PIMART can enable pharmacists to start

Aspect	PIMART	NSP 2023-2028
Objective	Expands the role of trained pharmacists to initiate and manage ART, including PrEP and PEP.	Aims to eliminate HIV, TB, and STIs as public health threats by 2030 through comprehensive prevention, treatment, and care strategies.
Equitable Access to Treatment	Decentralises HIV treatment by allowing pharmacists to initiate ART without requiring a doctor's referral, increasing access in underserved areas.	Seeks to ensure universal and equitable access to prevention, treatment, care, and support for HIV, TB, and STIs.
Task-Shifting & Workforce Efficiency	Reduces the burden on doctors and clinics by enabling pharmacists to provide ART, PrEP, and PEP, addressing healthcare worker shortage concerns.	Promotes task-shifting by allowing non-physician healthcare providers to take on more responsibilities, increasing service delivery.
Community-Based Care	Brings HIV prevention and treatment services closer to communities by allowing pharmacies to serve as access points.	Supports community-led HIV, TB, and STI responses by strengthening decentralised service delivery models.
Early Diagnosis & Prompt Treatment	Pharmacists can diagnose HIV and initiate ART immediately, reducing delays in treatment initiation and improving health outcomes.	Prioritises early diagnosis and immediate treatment initiation to improve health outcomes and prevent disease progression.
Reducing Stigma & Discrimination	Offers a discreet and accessible, environment for HIV services in pharmacies, helping to reduce stigma associated with seeking care in public clinics.	Aims to address stigma and discrimination as barriers to healthcare access, particularly for key populations.
Public-Private Partnerships & Collaboration	Represents an association between the private pharmacy sector and public health initiatives to expand ART coverage and enhance HIV care accessibility.	Encourages multi-sectoral collaboration, including private sector involvement, to strengthen healthcare service delivery.
Alignment with UNAIDS 95-95-95 Targets	Contributes to achieving the 95-95-95 targets by increasing ART access through pharmacies, improving early diagnosis, and ensuring treatment adherence.	Directly aligns with the UNAIDS 95-95-95 strategy by emphasising universal access to HIV prevention, treatment, and support services.
Scalability & Sustainability	Can be expanded nationwide in pharmacies, to improve ART coverage, especially in rural and underserved areas.	Focuses on sustainable HIV, TB, and STI prevention and treatment programs nationally, to ensure long-term impact.
Alignment with National Health Goals	By expanding access to ART and integrating services, PIMART supports South Africa's national strategy.	Contributes to South Africa's broader health objectives, which includes eliminating HIV, TB, and STIs as public health threats by 2030.

Figure 1: Comparison between PIMART and NSP

ART without a doctor's referral, speeding up treatment and reducing delays.

The NSP 2023-2028 aims to reduce stigma as a barrier to HIV care. PIMART can provide discreet and accessible HIV services at pharmacies, which may be less intimidating than clinics.

The NSP advocates for multi-sectoral collaboration, which includes the involvement of private healthcare providers. PIMART is in essence a public-private partnership where pharmacists collaborate with government health programs to enhance ART coverage. Both initiatives acknowledge the significance of service integration and collaboration across multiple sectors to tackle the complex factors affecting HIV, TB, and STIs. PIMART integrates HIV treatment into pharmacy-based care, while the NSP 2023-2028, presents a broad, multi-sectoral strategy with stakeholders to eliminate HIV, and TB as public health threats by 2030.

In terms of decentralised care, both PIMART and the NSP 2023-2028 emphasise bringing healthcare services closer to communities. PIMART enables trained pharmacists to initiate and manage ART, thereby decentralising HIV treatment and increasing accessibility, especially in underserved areas. Similarly, the NSP 2023-2028 focuses on community-centred interventions to reduce barriers and enhance access to care and treatment services.[12]

It can therefore be presumed that PIMART and the NSP 2023–2028 are aligned in their goals to decentralise care, optimise human resources, integrate services, promote equity, and achieve national health targets. Their collaborative efforts could be pivotal in advancing South Africa's response to HIV, TB, and STIs.

Expected Outcomes of Expanding PIMART Services in Communities

Expanding PIMART services to all underserved areas improves healthcare access, and would assist by addressing issues such as limited infrastructure, reducing long travel distances for patients, and alleviating health worker shortages. Providing pharmacy-led HIV services, including testing, early ART initiation, and access to PrEP and PEP, ensures timely, decentralised care. The outcomes include increased HIV diagnoses, better treatment adherence, reduced clinic congestion, and enhanced disease detection. Lower HIV transmission rates improve patient outcomes and contribute to a more resilient healthcare system. It is proposed that by implementing the rollout of PIMART, there would be potential direct and indirect benefits.

Expected Direct Outcomes

Increased HIV Diagnosis and Early ART Initiation

Expanding PIMART services will improve access to HIV testing, ensuring that individuals in remote communities receive timely diagnosis. Early identification of HIV-positive individuals will facilitate prompt initiation of antiretroviral therapy (ART), improving health outcomes and reducing disease progression. This can be done through work with community health workers to distribute test kits door-to-door, set up mobile pharmacy units to reach remote areas, and by offering testing days at local churches and schools to improve access. By expanding the availability of HIV testing, PEP, and PrEP in pharmacies, individuals at risk will have increased access to preventative measures. This will result in a decline in new infections, particularly among key populations such as young adults, pregnant women, and high-risk groups.

Improved Adherence to ART and PrEP, Reducing HIV Transmission Rates

Pharmacist-led interventions can provide continuous support, counselling, and adherence monitoring for patients on ART and pre-exposure prophylaxis (PrEP). This pro-active approach will enhance patient compliance, leading to reduced viral loads and lower transmission rates within communities. This can be done through PIMART-trained pharmacists initiating and dispensing PEP, PrEP, and first-line ART, providing adherence counselling and follow-up services to ensure treatment success. Establishing rapid response PEP centres for sexual assault and occupational exposure cases would also contribute to reducing infection and transmission rates. Although no statistics are available in this regard, further investigation into this proposal would be of benefit to studies.

Increased ART Adherence Due to Pharmacist-Led Support and Counselling

Integrating pharmacists into HIV care improves patient education, dispels misconceptions about ART, and personalises treatment. Pharmacist-led adherence programs reduce treatment interruptions and enhance patient health. Developing telehealth platforms that allow pharmacists to offer virtual support, and counselling could improve ART adherence, PrEP, PEP and STI management. To further strengthen access to pharmacist-led telehealth services, pharmaceutical associations can collaborate with mobile network providers to offer free or subsidised data access for healthcare consultations. This initiative would remove financial barriers to digital healthcare access, ensuring that underserved populations can benefit from remote pharmacist support. Such partnerships could also facilitate the development of mobile applications that integrate medication reminders, educational resources, and direct communication with pharmacists, enhancing patient engagement and long-term adherence.

Expected Indirect Outcomes

Greater Uptake of Self-Testing Kits, Leading to Early Detection of HIV and STIs

Increased awareness and availability of self-testing kits at community pharmacies will encourage individuals to assess for HIV and sexually transmitted infections (STIs) in private settings. Early detection will enable timely medical intervention, reducing the spread of infections.

Reduced Healthcare Facility Congestion Through Decentralised Pharmacy-Led Services

By adding services like HIV testing, ART initiation, and PrEP distribution to pharmacies, the burden on overburdened clinics and hospitals will decrease. This will allow healthcare facilities to focus on critical and complex cases, optimising resource allocation.

Enhanced Digital Healthcare Access, Bridging Gaps in Health Infrastructure

The adoption of digital health tools, including electronic health records and mobile applications, will enhance communication between pharmacists and other healthcare providers. This will enable seamless patient follow-ups, improve remote monitoring, and optimise overall healthcare delivery. Telehealth consultations can be implemented to support individuals unable to visit clinics, while pharmacies can serve as telehealth hubs where patients access virtual doctor consultations and confidential counselling and support for HIV, STIs, PrEP, and ART adherence. Incorporating Digital solutions into PIMART services will allow patients easier access to care

Additionally, accessible online platforms can be developed for self-screening of HIV, TB, STIs, and common mental health conditions, with pharmacists trained to guide patients in using these tools and interpreting results. Integrating referral systems within digital platforms can help connect high-risk individuals to appropriate healthcare services. Moreover, digital solutions such as medication adherence apps and virtual counselling will enhance patient engagement and ensure continuity of care.

Improved Early Detection of STIs, TB, and Pregnancy, Reducing Complications

Pharmacies will serve as key access points for rapid diagnostic tests, enabling the early identification of STIs, TB infections, and pregnancy. Early intervention will lead to better health outcomes, reduced transmission, and improved maternal and child health.

Figures 2 and 3 summarises the expected direct and indirect outcomes of providing PIMART services in communities.

The implementation and enhancement of PIMART services is anticipated to result in significant improvements in healthcare accessibility, a reduction in disease burden, and an overall increase in the quality of life for underserved populations. Integrating PIMART into the healthcare system will allow for enhanced service delivery, reduced pressure on traditional healthcare facilities, and ensure that a greater number of individuals receive timely HIV prevention and treatment services. This will also contribute directly to the objectives of the NSP 2023-2028.[7, 8, 9]

Implementation Strategies to increase support for PIMART

Implementing PIMART in South Africa can enhance ART access, particularly in underserved areas. The success of this implementation relies on progressive policy reforms, continuous pharmacist training, digital health integration, community engagement, financial support, and strong monitoring systems. Addressing these key areas could strengthen South Africa's HIV response and contribute to achieving the UNAIDS 95-95-95 targets. South Africa has a high HIV prevalence rate, with approximately 7.8 million individuals living with HIV in 2023/2024. The following are proposed implementation strategies:

Policy and Regulatory Support

Updating regulations to officially authorise PIMART-trained pharmacists for ART services and establish standard procedures for HIV management as proposed by BN 101 of 2021. This board notice stipulates the scope of practice, competency standards and

Increased HIV Diagnosis and Early ART Initiation	Expanding PIMART services increases HIV testing access in remote areas. Early diagnosis leads to prompt ART initiation, improving health outcomes. Community health workers distribute test kits; mobile pharmacy units reach remote locations. Testing at local churches and schools improves accessibility. Increased access to PEP and PrEP lowers new HIV infections, particularly among key populations.
Improved Adherence to ART and PrEP, Reducing HIV Transmission Rates	Pharmacist-led interventions provide adherence support and monitoring. Lower viral loads lead to reduced HIV transmission. PIMART-trained pharmacists initiate and dispense ART, PrEP and PEP. Rapid response PEP centres can address sexual assault and occupational exposure cases.
Increased ART Adherence Due to Pharmacist-Led Support and Counselling	Pharmacist involvement improves patient education and dispels ART misconceptions. Telehealth platforms enable virtual pharmacist support for ART, PrEP and PEP. Collaborations with mobile networks offer subsidised data access for healthcare consultations. Mobile apps integrate medication reminders, educational resources and direct pharmacist communication.

Figure 2: Expected DIRECT outcomes of PIMART rollout - summary

Greater Uptake of Self-Testing Kits, Leading to Early Detection of HIV and STIs	Increased awareness and availability of self-testing kits promote private HIV and STI assessments. Early detection enables timely medical intervention and reduces infection spread.
Reduced Healthcare Facility Congestion Through Decentralised Pharmacy-Led Services	Pharmacy-based HIV testing, ART initiation, and PrEP distribution reduce strain on clinics. Allows hospitals to focus on critical and complex cases.
Enhanced Digital Healthcare Access, Bridging Gaps in Health Infrastructure	Digital tools (electronic health records, mobile apps) improve pharmacist-provider communication. Telehealth consultations support patients unable to visit clinics. Pharmacies serve as telehealth hubs for virtual doctor consultations and counselling. Online platforms enable self-screening for HIV, TB, STIs, and mental health conditions. Digital referral systems connect high-risk individuals to healthcare services.
Improved Early Detection of STIs, TB, and Pregnancy, Reducing Complications	Pharmacies provide rapid diagnostic tests for STI, TB, and pregnancy screening. Early intervention improves health outcomes, reduces transmission, and enhances maternal-child health.

Figure 3: Expected INDIRECT outcomes of PIMART rollout - summary

Strategy	Details
1. Policy and Regulatory Support	Update regulations to authorise PIMART-trained pharmacists for ART services. Implement BN 101 of 2021, outlining scope, competency standards, and accreditation criteria.
2. Capacity Building and Training	Pharmacists need to include self-testing, ART initiation, and virtual care. Provide ongoing training on updated ART/STI protocols (PHC STG & EML). Develop digital systems for data recording and integration. Use mobile health apps, telemedicine, and e-prescription tools for better patient management.
3. Provide Digital Support	Advanced digital systems, mobile health apps, telemedicine services, and electronic prescription tools can enhance pharmacist data sharing, patient follow-ups, adherence monitoring, and ART dispensing efficiency.
4. Supply Chain Management	Strengthen ART procurement and distribution to avoid stockouts. Use demand forecasting tools to predict medication needs in pharmacies.
5. Community Engagement and Awareness	Promote pharmacy-led HIV services through public campaigns and media outreach (e.g., SMS, radio). Involve community leaders and train CHWs to refer patients to PIMART-participating pharmacies.
6. Financial Support	Secure funding from government and international donors by emphasising the alignment of PIMART with South Africa's HIV targets. Establish financial and professional incentives for pharmacists, although formal structures are currently lacking.
7. Monitoring and Evaluation	Implement systems for data tracking, periodic reviews, and assessments of pharmacist performance to measure the impact and effectiveness of PIMART services.

Figure 4: Implementation strategies to increase support for PIMART - summary

the criteria for accreditation of a PIMART course. Although initial approvals were granted, ongoing legal challenges have postponed the implementation of PIMART. The Independent Practitioners Association Foundation (IPAF) appealed a High Court decision in favour of PIMART, emphasising the continuing legal deliberations.[10]

Capacity Building, and Training

Capacity building and training are essential to ensure that pharmacists are clinically competent and confident in initiating and managing antiretroviral therapy. Training improves the quality and safety of care, promotes consistent service delivery. Whilst the curriculum is comprehensive, tools such as self-testing, virtual care, and ongoing training on updated ART and STI management protocols based on the PHC STG and EML will be beneficial for implementation.[13]

Provide digital support

Develop newer and advanced digital systems that allow pharmacists to record patient data and share it with government health, and other third-party role players' information systems. Use existing mobile apps and implement new mobile health apps and support for telemedicine services will further enhance implementation strategies. These services could also assist in patient follow-ups and adherence monitoring. Another useful tool can be to use electronic prescription systems to track ART dispensing and prevent duplication or misuse.

Supply Chain Management

To support supply chain management, strengthening ART procurement and distribution systems to prevent stockouts, and implementing demand forecasting tools will assist in predicting ART medication needs in pharmacies. Precise forecasting of ART medication demand is necessary for ensuring sufficient stock levels and preventing shortages or wastage. This includes creating reliable supply chains to community pharmacies, improving communication with central stock systems, and maintaining consistent, timely transportation methods.

Community Engagement and Awareness

Promote pharmacy-led services through public campaigns, involve community leaders, and use SMS/radio outreach to educate outlying populations. Train Community Health Workers (CHWs) to refer patients to PIMART pharmacies.

Financial support

Securing funding from government and international donors is vital for sustaining PIMART services. PIMART will align with South Africa's commitment to global HIV targets and can potentially attract international support. Providing financial and professional incentives can encourage pharmacist participation in PIMART, though specific incentive structures do not yet exist.

Monitoring and Evaluation

Implement data tracking, periodic reviews, and pharmacist performance assessments to ensure the effectiveness of PIMART services.[10]

Conclusion

The implementation of PIMART services, provides a new approach that will significantly enhance access to HIV prevention, diagnosis, and treatment. By allowing PIMART-trained pharmacists to contribute, we can develop a more inclusive, efficient, and patient-centred healthcare system within our resource-constrained health landscape. It aligns with South Africa's National Strategic Plan (2023–2028) and the UNAIDS 95-95-95 goals, suggesting it could serve as a model for decentralised healthcare. Stakeholders, including government health departments, regulatory bodies, pharmaceutical associations, and community organisations, should collaborate to implement and scale up PIMART services nationwide. A co-ordinated effort will ensure that all populations receive the life-saving care they require and contribute to the fight against HIV, TB and STIs.

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SAAHIP 68th Annual General Meeting and 37th Annual Conference 2025

Rashmi Gosai
SAAHIP SG Branch Chair/Conference Convener

"Future Ready 5.0"

Empowering Hospital Pharmacists for Tomorrow's Healthcare Revolution

Introduction

The South African Association of Hospital and Institutional Pharmacists (SAAHIP) hosted its 37th Annual Conference and 68th Annual General Meeting from 10–12 April 2025 at the breathtaking Champagne Sports Resort in the Drakensberg. Themed *"Future Ready 5.0 – Empowering Hospital Pharmacists for Tomorrow's Healthcare Revolution"*, the SAAHIP Southern Gauteng Branch was tasked to convene the event, which brought together nearly 200 attendees from across South Africa, representing public and private sector hospitals, universities, hospital groups, and pharmaceutical companies.

This diverse gathering of healthcare professionals, academics, and industry leaders fostered a dynamic environment of collaboration, critical thinking, and shared purpose as delegates explored the evolving role of hospital pharmacists in an era of rapid technological advancement and national health reform.

Theme Context

As the global healthcare environment rapidly transitions into the Fifth Industrial Revolution—a phase defined by the integration of artificial intelligence (AI), automation, and human-centred design—hospital pharmacists are called upon to lead change, enhance system resilience, and deliver compassionate care through technology-enabled solutions.

The conference addressed the need for adaptability, innovation, and collaboration as essential qualities for future-ready pharmacists in both public and private sectors, particularly in the context of South Africa's healthcare reform under the National Health Insurance (NHI).

Academic Programme Highlights

The academic programme was a key strength of the conference, offering over 40 sessions in the form of podium, poster, pearl, and scenario presentations. These sessions delivered evidence-based insights, showcased service delivery improvements, and encouraged professional dialogue around systemic healthcare challenges.

Themes Explored:

- Digital Health & Automation

- NHI Readiness & Policy

- Antimicrobial Stewardship

- Clinical Governance & Risk Mitigation

- Human-Centred Leadership

Presentation Formats:

- Podium

- Poster

- Pearl

- Scenario

Notable presentations included Pharmacist leadership in NHI, Antimicrobial stewardship, Resilience in reform, Tech-Driven Innovation, Patient-Centric Solutions, AI & Automation in Practice, Data-Enabled Care, Interdisciplinary Collaboration, Smart Supply Chains, Digital Health Integration, Empowered Pharmacists, Sustainable Healthcare Models, Visionary Leadership.

Academic Award Winners:

- The Life Healthcare Best Poster Presentation Award: Telicia Jobraj
- The Life Healthcare Best Podium Presentation Award: Vivian Chengalroyan
- The Adcock Ingram Best Pearl Presentation Award: Kristien Schutte
- The Mediclinic Best Scenario Presentation Award: Bandela Mgoqi
- Best Academic Presentation Overall Award: Prof Renier Coetzee

Keynote & Invited Guests

The programme featured inspiring contributions from key figures and organisations:

- Motivational Speaker – Anthea van den Bergh: Delivered a rousing address on empathy, courage and innovation in healthcare leadership
- Marketing Code Authority – Valerie Beaumont: Addressed ethical medicine promotion
- South African Health Products Regulatory Authority (SAHPRA) – Audrey Chigome: Shared updates on medicine regulation and pharmacovigilance
- South African Pharmacy Council (SAPC) – Vincent Tlala: Reinforced ethics, CPD, and professional growth
- Pharmaceutical Society of South Africa (PSSA) – Tshifhiwa Rabali: Advocated for pharmacists' strategic role in national healthcare

These engagements added valuable context and policy alignment to the academic and professional programme.

Additional Highlights:

Nicole Keuler, a lecturer at the University of the Western Cape, delivered a compelling presentation on pharmacogenomics, highlighting how personalised medicine can optimise therapeutic outcomes and reduce adverse drug reactions by tailoring treatment to an individual's genetic profile.

The Young Pharmacists' Group (YPG) Chair, Ntombizodwa Luwaca, made a strong impression with her energy and engagement contributing fresh perspectives and reinforcing the importance of youth leadership in the future of hospital pharmacy.

Social Programme & Engagement

Evening events provided valuable opportunities for networking and celebration. From themed dinners to the elegant Gala Dinner, delegates enjoyed relaxed and vibrant settings to strengthen professional and personal connections.

- Evening 1 – Futuristic: Sponsored by Fresenius Kabi, this themed event set the tone for innovation and imagination as delegates embraced a vision of pharmacy in the years ahead.
- Evening 2 – Pathfinders: Sponsored by Equity Pharmaceuticals, this celebration honoured the pioneers of pharmacy and encouraged delegates to continue charting new frontiers.
- Gala Dinner – Around the World in 80 Days (City Life Edit): Sponsored by SAAHIP, the elegant gala offered a global journey through music, cuisine, and culture, bringing delegates together in style to close off the conference on a high note.

Other Awards & Recognition

Branch Awards

- Membership Award: Limpopo
- Spirit Award: Limpopo

Trade Awards:

- Best Appearance: Adcock Ingram
- Best Hospitality: Equity Pharmaceuticals
- Most Informative: Equity Pharmaceuticals
- Best Trade Overall (Delegate Vote): Adcock Ingram

Scavenger hunt winner – Western Cape

Trade bingo winner – Trinia Mafarafara

Most creative gala dinner table setting – Paris by Northern Gauteng

SAAHIP National Executive Committee(2025/2026)

Top: Left to right

Shawn Zeelie (Free-state/Northern Cape); Handsome Mashego (Mpumalanga); Kesentseng Mahlaba (Northern Gauteng); Vusi Dhlamini (KZN - Inland & newly elected Vice President); Joggie Hattingh (Western Cape)

Bottom: Left to right

Ignatius Muller (North-West); Samukelisiwe Matibela (KZN- Coastal), Salome Mabule (Limpopo); Nomfundo Zwane (Mpumalanga & re-elected Treasurer); Nhlanhla Mafarafara (Limpopo & Immediate Past President); Seshnee Moodley (Eastern Cape & Newly elected President); Caroline De Beer (Western Cape & re-elected Secretary); Rashmi Gosai (Southern Gauteng); Robyn Wates (Eastern Cape)

Annual General Meeting

The 68th AGM addressed governance, advocacy, and member development. The newly elected Presidential Committee for 2025 is:

- President: Seshnee Moodley
- Vice-President: Vusi Dhlamini
- Secretary: Caroline De Beer
- Treasurer: Nomfundo Zwane
- Immediate Past President: Nhlanhla Mafarafara

Trade sponsorship

The conference would not be possible without the continued support of our trade partners: Adcock Ingram Critical Care for registration, Fresenius Kabi for the Thursday evening event, Equity Pharmaceuticals for the Friday evening event, Pharma Dynamics for room drops, teas, and shared sponsorship of lunches, Sanofi and Viatris for their contributions towards the lunches, Aurogen for sponsoring the breakfasts.

Exhibitors: Adcock Ingram, Bayer, AstraZeneca, Biovac, Equity Pharmaceuticals, Fresenius Kabi, National Bioproducts Institute, Novo Nordisk, Novartis, Vital Life, Sanofi, Dr. Temp, SAHPRA, and the South African Pharmacy Council – thank you for your valued presence and support.

Conclusion

The SAAHIP 2025 Conference – Future Ready 5.0 – was not just an event, but a powerful reaffirmation of the value, voice, and vision of hospital pharmacists in shaping the future of healthcare in South Africa. Through inspiring academic presentations, dynamic industry collaboration, and meaningful policy dialogue, delegates left not only informed but transformed.

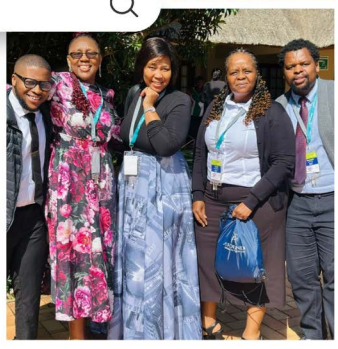
The conference affirmed that the hospital pharmacist of tomorrow is already emerging today—innovative, adaptable, compassionate, and committed to equitable healthcare. As we stand on the brink of systemic reform and technological evolution, it is clear: the future is not something to brace for—it is something we are ready to lead.

Together, we are not just prepared for the future—we are the force shaping it.

SAAHIP Delegations – Highlights in photos

Eastern Cape

KZN Coastal



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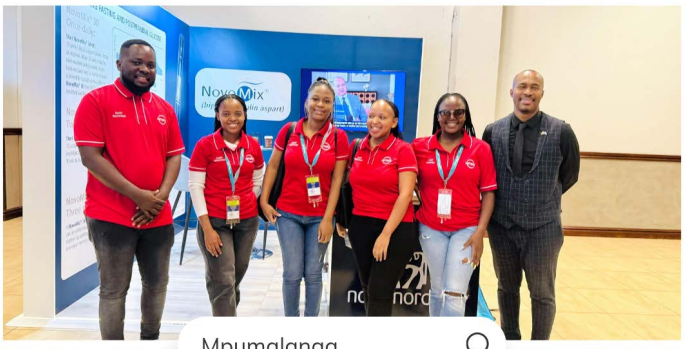
Southern Gauteng



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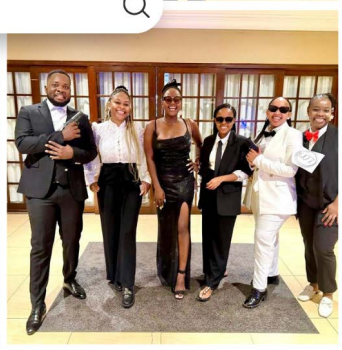


Conference Organizing Committee:
Left to right: Tabassum Shaik, Thanushya Pillaye, Rashmi Gosai, Sheila Valla
Absent: Jacquie Fox & Liezl Nightingale

"Keep your eyes on the stars, and your feet on the ground" ~ Theodore Roosevelt

Dr Seshnee Moodley
President, SAAHIP

The above quote reminds one to always aim high and to reach for greatness in all that we do. However, in doing so, we should strive to work hard whilst staying grounded and balanced. Being a pharmacist is almost an intrinsic calling where one has the strong desire to make a positive difference in a person's life. As healthcare workers, we have such important roles to play and we should always value these positions.

I am deeply humbled and grateful to SAAHIP in electing me to the position of President. I commit to leading with excellence, passion, compassion, devotion and to the best of my ability. During our national SAAHIP conference (April 2025), delegates were exposed to a brilliant keynote speaker, Anthea van den Berg, who started the conference on a high note. She covered the topic of personal branding and telling our 'stories', because often we are so busy delivering services, we forget to highlight our achievements and what it is, that Pharmacists actually do.

The previous SAAHIP Presidential team set out their term with 4 important pillars and as the current president of SAAHIP, I want to move forward with these pillars i.e. collaboration, shared vision, commitment and embracing innovation. This speaks to me as a pharmacist and therefore, I fully endeavour to carry this vision through, improving and building on it. For us to surge ahead in the healthcare space, we need to move together in unison, support each other and ensure that all cadres of pharmacy in both public and private settings are fully engaged and included.

The pharmacy profession is rapidly evolving. The practice of pharmacy or the pharmacists' role has changed from the days of the apothecary, where compounding of medicines took place, followed by handing of these medicines to the patient or those requesting it, with a sprinkling of medical advice. Most of the evidence used was based on trial and error. Currently, pharmacists are recognised healthcare professionals, who are part of multi-disciplinary teams, delivering expert medicine advice both to patients and other healthcare workers, ensuring therapeutic goals are achieved in evidence-based ways.

The World Health Organisation (WHO), responsible for global health, developed the 7-star pharmacist concept (2014) to provide a framework/understanding of what a pharmacist is. It describes the roles, responsibilities, skill sets and even qualities that a pharmacist should possess. The 7-star pharmacist is a leader, teacher, lifelong learner, caregiver, decision maker, communicator and manager. More recently this has evolved to the 10-star pharmacist, to add on researcher, entrepreneur and team player. A 10-star pharmacist is so much more than just providing medication to a patient. I believe it is important to always remind ourselves what the responsibilities/roles of 10-star pharmacist should be:

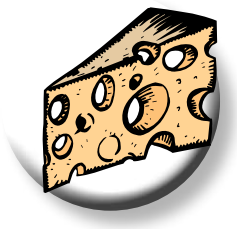
Dr Seshnee Moodley

1. **Researcher** – a pharmacist must practice evidence-based care ensuring that best care is given to patients. A pharmacist may be part of drug utilisation studies or drug-development research or be involved in policy development, which may contribute to the overall current body of pharmaceutical knowledge and expertise.
2. **Communicator** – The pharmacist plays an integral role in communicating medicine- and disease-related information effectively to the patient. We are key role players in the multi-disciplinary team and also responsible for communication with other stakeholders.
3. **Caregiver** – The pharmacist must always put the patient and the agreed goal of therapy first.
4. **Decision maker** – A pharmacist must be able to think quickly and rationally, and this may involve patient's therapy or care, drug budgets or ethical considerations.
5. **Lifelong learner** – When you become a pharmacist, you will be learning forever. The profession is dynamic and we need to stay abreast of pharmacy topics, new research, new healthcare strategies, technology and methods to enhance our practice.
6. **Teacher** – Pharmacists must mentor the future of the profession i.e. young pharmacists and pharmacy associate staff. We are also in strategic positions to educate other healthcare professionals, by imparting our knowledge to them.
7. **Entrepreneur** – We should be able to come up with novel pharmaceutical ideas, quality improvement projects, and drug research ideas and develop plans for enhanced operations within the healthcare sector.

8. **Leader** – We are responsible for training both the young pharmacists and the associate staff and being their leader. We are constantly in positions of leadership in the multi-disciplinary teams and we should lead with grace.
9. **Manager** – Pharmacists must manage resources, staff, patients' wellbeing and overall co-ordination of pharmaceutical knowledge and information, according to the prescribed guidelines.
10. **Team Player** – We need to support colleagues, collaborate and be part of the team. Being a pharmacist requires you to be adaptable and ready for change/challenges.

A pharmacist is an integral part of the healthcare system. We are responsible for the provision of quality healthcare to patients and are the custodians of medicine. Our medicines expertise sets us apart from other healthcare professionals. It is indeed time for us to solidify our place again in healthcare by practicing being 10-star pharmacists. As pharmacists our roles are so diverse, yet so incredibly rewarding. Tell your story, increase your visibility, and own your pharmaceutical space. Theodore Roosevelt's quote above urged us to aim high but remain grounded. I urge you, my fellow pharmacists and colleagues to always keep your eyes on the stars, just remember for pharmacists, there are always '10'!

I look forward to the opportunity of leading, together with my National Executive committee, the South African Association of Hospital and Institutional Pharmacists.



Nibbles

What's in a name?

At least fifty years ago, before the world of pharmacy had to adapt to the growing presence of large corporates, and decades before the advent of computers and scanners in pharmacy, a community pharmacist was expected to know all his clients by name. Furthermore, when you got the call for a repeat prescription, it would invariably be along the lines of, *"Ask Mr Black for more of my pills, please, but only the white ones, not the little pink ones for under the tongue, I still have enough of those, OK?"* You, as the pharmacist, were expected to know exactly what they were talking about!

In my father's pharmacy, Tarka Pharmacy, which served a large farming community, things went a step further. The farming families had been there for many generations and the farms were traditionally handed down from father to eldest son. Usually the son also inherited the father's name so you would need to distinguish whether you were speaking to the senior or junior of the two. The next problem was that there would be cousins bearing the same name. For example, there were at least two Harry van Heerdens. The solution to this dilemma was to distinguish them by the names of their farms so that you had Harry van Heerden, *Middelkraal* and Harry van Heerden, *Schaapkraal*. Their parcels for collection were labelled accordingly and you had to be careful in checking that the right parcel (and account) went to the right Harry van Heerden!

About thirty years ago, while working as a community pharmacist, I had my own interesting experiences, one of which was the following…

Our client, Mrs V, was a kindly soul but rather simple. Some would contend that, in her case, the lift did not quite go all the way up to the top floor! She was large, loud and brash. Mean folk would call her *"common"*. She was actually kind and generous in her own way and her pharmacy account was often in arrears, not from buying niceties for herself, but rather medicine for her grandchildren and gifts for friends. Her command of *"die Ingelsman se taal"* was not great and one had to listen closely to understand exactly what she was requesting.

When Mrs V came to town, you could hear her a mile away as she strode the main road, cheerfully greeting all and sundry at the top of her booming voice. In her tent-like dress, usually of a loud, gory colour, and large enough to cover her bountiful body, she strutted down the road like a clucking mother-hen with a number of her grandchildren in tow. When she swept into the pharmacy with her entourage, she would greet everybody with a huge smile and a loud broadcast of, *"Hello peoples!"* Her mere presence filled the entire pharmacy whilst our staff needed to be on full alert watching the grandchildren running amok between the aisles.

Then one day it happened…Mrs V, at the top of her booming voice, loud enough for the whole pharmacy to hear, asked our front shop assistant,

"*Ag, Bokkie, just ask the chemist to give me some more of my **vagina** pills, please!"*

A number of other clients of a more genteel nature, now rather embarrassed, shuffled hastily along out of the way, pretending not to hear.

When our assistant gave Mrs V a puzzled look and politely asked her to repeat her request, she said, patting her more than ample bosom,

"Ag, bokkie, you know mos, my vagina pills for the pains in my chest, man!"

Having heard this loud request all the way from the dispensary, I could hardly contain myself as I went about dispensing Mrs V's monthly supply of ***angina*** tablets without further question!

But, then again, as The Bard wrote;

"*What's in a name? That which we call a rose*

By any other name would smell as sweet."

Ek sê maar net!

Gary Black

Pharma Dynamics launches Calsar co – a new standard in triple combination antihypertensive therapy

pharma dynamics
EFFECTIVE AFFORDABLE HEALTHCARE

Pharma Dynamics has announced the launch of Calsar Co, a fixed-dose triple combination therapy formulated with amlodipine, valsartan and hydrochlorothiazide (HCTZ). This once-daily tablet is used to treat high blood pressure in patients whose blood pressure has been stabilised on the combination of the three medicines given as individual doses, at the same time.

"In line with evolving hypertension treatment strategies, Calsar Co, brings evidence-based triple therapy to the forefront of primary care," says Ingrid Singels, Marketing Manager of Pharma Dynamics' Scientific Division. "Our goal is to improve blood pressure control rates by making it easier for clinicians to uptitrate treatment conveniently."

Calsar Co is available in five dosage strengths: 5/160/12.5 mg, 5/160/25 mg, 10/160/12.5 mg, 10/160/25 mg and 10/320/25 mg. Each tablet contains a calcium channel blocker (amlodipine), an angiotensin receptor blocker (valsartan) and a thiazide diuretic (HCTZ), which collectively target different physiological mechanisms contributing to hypertension.

A landmark randomised clinical trial by Calhoun et al. (2009) demonstrated that the triple combination of amlodipine/valsartan/HCTZ significantly reduced mean sitting systolic and diastolic blood pressure (BP) compared to any dual therapy arm (all $p < 0.0001$). Notably, a greater proportion of patients on triple therapy achieved the target BP of < 140/90 mmHg ($p < 0.0001$), with benefits consistent across age, sex, race and baseline blood pressure subgroups.

According to the 2023 European Society of Hypertension (ESH) Guidelines for the management of arterial hypertension, low-dose triple combination therapy is a recommendation when dual therapy fails to control blood pressure. This approach is especially relevant for patients with BP ≥ 150/95 mmHg or those at high cardiovascular risk. Triple therapy has been shown to control blood pressure in up to 90% of patients, with fixed-dose single-pill combinations offering superior outcomes compared to usual care. However, initial treatment with triple therapy is generally avoided due to the potential for overly rapid or excessive BP reduction, particularly in older adults.

"Calsar Co aligns with best-practice guidelines by combining three complementary agents into one pill, potentially improving adherence and persistence," notes Singels. "This is crucial, given the high pill burden often associated with multidrug antihypertensive regimens."

Bioequivalence studies confirmed that Calsar Co achieves comparable plasma concentrations to the originator brand across all three active ingredients (amlodipine, valsartan and HCTZ), with 90% confidence intervals well within the accepted bioequivalence range.

In addition to its clinical value, Calsar Co is priced up to 58% lower than the originator, with a single exit price (SEP) for the 10/320/25 mg formulation listed at R259.83 excl VAT. This significantly enhances accessibility, particularly in South Africa's cost-sensitive healthcare environment.

Singels emphasises the importance of escalating therapy in patients who remain uncontrolled on dual agents. "For those with apparent resistant hypertension or target organ damage, timely intensification can reduce cardiovascular events and improve long-term outcomes."

Recognising the multidimensional nature of hypertension, Pharma Dynamics also offers educational resources to support dietary and lifestyle interventions. These include low-salt recipe guides and patient adherence tools, all accessible via QR codes on packaging.

"Combining pharmacological treatment with lifestyle support improves outcomes exponentially," she adds. "Our patient-centred approach extends beyond the tablet itself."

Calsar Co reflects a modern approach to hypertension management – harnessing the efficacy of evidence-backed combination therapy in a cost-effective, once-daily tablet.

For more information or prescribing details, contact Pharma Dynamics at info@pharmadynamics.co.za or visit www.pharmadynamics.co.za

sapj

CPD questionnaire • July/August

Heart failure: understanding the condition and navigating its management

1. Which of the following is a hallmark symptom of heart failure with reduced ejection fraction (HFrEF)?

a Bradycardia
b Peripheral oedema
c Hyperglycaemia
d Hypotension

2. What is the primary role of beta-blockers in the management of heart failure?

a Increase cardiac output
b Reduce fluid overload
c Lower myocardial oxygen demand and prevent arrhythmias
d Enhance renal function

3. Which of the following medications has been shown to reduce mortality in patients with HFrEF?

a Digoxin
b Furosemide
c Sacubitril/valsartan
d Atorvastatin

The role of pharmacists in optimising patient outcomes to reduce the burden of tonsillitis

4. Which of the following statements about the aetiology of tonsillitis is correct?

a Bacterial tonsillitis is more commonly caused by *Haemophilus influenzae* than *Streptococcus pyogenes*
b *Streptococcus pyogenes* infections are always preventable with antibiotics
c Viral infections account for the majority of tonsillitis cases
d *Mycobacterium tuberculosis* is a typical acute cause of tonsillitis in children
e *Corynebacterium diphtheriae* is a frequent pathogen in vaccinated populations

5. Which of the following treatment strategies is most appropriate for a patient with confirmed streptococcal tonsillitis and a Type 1 penicillin allergy?

a Phenoxymethylpenicillin for 10 days
b Cephalexin for 5–7 days
c Azithromycin for 3–5 days
d Amoxicillin for 7 days
e Benzathine penicillin G IM single dose

6. Which of the following statements regarding antimicrobial resistance (AMR) in tonsillitis is TRUE?

a Resistance in *S. pyogenes* is primarily due to beta-lactamase production.
b Topical antibiotics like neomycin are always safe to use for sore throat.
c Macrolide resistance is decreasing globally due to shorter treatment durations.
d Co-pathogens like *S. aureus* can contribute to treatment failure by inactivating penicillin.
e Penicillin resistance in *S. pyogenes* is due to its ability to mutate penicillin-binding proteins.

Advances in hypothyroidism management: rethinking therapy beyond levothyroxine

7. Which of the following is a common symptom of hypothyroidism in adults?

a Rapid heart rate
b Heat intolerance
c Weight gain and fatigue
d Increased appetite

8. Which of the following is the most common cause of hypothyroidism in iodine-sufficient areas?

a Central hypothyroidism
b Graves' disease
c Hashimoto's thyroiditis
d Pituitary adenoma

9. What is the main reason that combination LT4+LT3 therapy is underutilised despite evidence of benefit in some patients?

a It is associated with a higher risk of cancer
b It lacks fixed-dose formulations that mimic natural hormone ratios
c It is significantly more expensive than LT4 monotherapy
d It is not approved in any country

Depression unveiled: a comprehensive review of pathophysiology and treatment advances

10. Which of the following best describes the monoamine hypothesis of depression?

a Depression is caused by excessive production of cortisol and other glucocorticoids.
b Depression results from deficits in serotonin, norepinephrine, and dopamine in key brain regions.
c Depression is due to overactivation of the glutamate and GABA systems.
d Depression is caused solely by genetic mutations in serotonin receptors.

11.	**Which neurotransmitter imbalance has been associated with elevated levels in the blood, brain, and cerebrospinal fluid of patients with depression?**
a	Dopamine
b	Glutamate
c	GABA
d	Acetylcholine
12.	**Which of the following antidepressant classes is considered first-line therapy due to its proven efficacy and safety profile?**
a	Monoamine oxidase inhibitors (MAOIs)
b	Tricyclic antidepressants (TCAs)
c	Selective serotonin reuptake inhibitors (SSRIs)
d	Benzodiazepines

SGLT2 inhibitors in type 2 diabetes mellitus: a pharmacist's guide to optimised care

13.	**Which of the following best explains the glucose-lowering action of SGLT2 inhibitors in type 2 diabetes mellitus (T2DM)?**
a	Increasing insulin secretion by pancreatic beta cells
b	Inhibiting hepatic glucose production
c	Delaying intestinal carbohydrate absorption
d	Enhancing urinary glucose excretion via inhibition of glucose reabsorption in the proximal tubule
e	Blocking glucagon receptors
14.	**Which clinical trial demonstrated a 38% reduction in cardiovascular mortality in high-risk T2DM patients treated with empagliflozin?**
a	DECLARE-TIMI 58
b	DAPA-CKD
c	EMPA-REG OUTCOME
d	CREDENCE
e	CANVAS
15.	**Which of the following medications is a UGT enzyme inducer that may reduce the plasma concentration and efficacy of SGLT2 inhibitors like dapagliflozin and canagliflozin?**
a	Paracetamol
b	Probenecid
c	Simvastatin
d	Valsartan
e	Rifampicin

Human papillomavirus (HPV) as the main cause of cervical and other related cancers: a review

16.	**Which two HPV types are most strongly associated with the development of cervical cancer?**
a	HPV-6 and HPV-11
b	HPV-16 and HPV-18
c	HPV-31 and HPV-45
d	HPV-52 and HPV-58
17.	**What is one of the key roles of pharmacists in managing HPV-related diseases, as discussed in the article?**
a	Performing surgical treatment for cervical cancer
b	Prescribing chemotherapy directly
c	Educating the public and managing vaccine supply
d	Diagnosing cancers through biopsy
18.	**What is a primary reason why HPV vaccination coverage remains low in some countries?**
a	Lack of effectiveness of the vaccine
b	Overabundance of screening programmes
c	High mutation rate of HPV strains
d	Barriers such as cost, infrastructure, and awareness

Interprofessional impressions amongst 4th-year medical and pharmacy students at Sefako Makgatho Health Sciences University

19.	**What was the primary aim of the Interprofessional Education and Collaborative Practice (IPECP) initiative described in the article?**
a	To evaluate clinical outcomes in private healthcare settings
b	To implement a standardised curriculum across all health professions
c	To provide health professions students with structured interprofessional collaborative practice exposure
d	To train pharmacists to work independently of other healthcare professionals
20.	**Which of the following BEST describes a key benefit of interprofessional collaborative practice highlighted in the article?**
a	Reduction in the duration of undergraduate education
b	Improved patient outcomes through coordinated care
c	Increased administrative efficiency for healthcare institutions
d	Elimination of the need for continuing professional development
21.	**What setting was used for the practice-based IPECP initiative?**
a	Hospital emergency department
b	Rural health clinic
c	Community-based service-learning site
d	University

The answers for these CPD questions will be in the upcoming issue of the SAPJ.
This activity can contribute towards your CPD compliance.

CPD answers • May/June 2025

1. c 2. b 3. b 4. c 5. c 6. c 7. b 8. c 9. d 10. a 11. d 12. c
13. a 14. d 15. b 16. c 17. b 18. c

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